Targeted Drug Repurposing in Precision Oncology Reveals Celecoxib as a GSK-3β Inhibitor in Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is a lethal cancer lacking effective targeted therapies. GSK-3β plays a pivotal role in oncogenic signaling in HCC. This study explores the potential of repurposing FDA-approved drugs targeting GSK-3β as a precision medicine approach, aiming to uncover novel therapeutic strategies through in silico molecular modeling. **Aim:** This study aimed to identify potential FDA-approved drugs that can be repurposed to inhibit GSK-3β using an in-silico precision medicine approach for HCC. **Methods:** The three-dimensional structure of GSK-3β (PDB ID: 1Q3W) was retrieved from the Protein Data Bank and prepared for docking simulations. Four FDA-approved candidate drugs-Celecoxib, Tideglusib, Metformin, and Lithium carbonate-were docked using AutoDock Vina integrated within PyRx. Toxicity profiles were predicted using the ProTox-II webserver. Additionally, functional enrichment and pathway analyses were performed using STRING v11.5 to identify key GO terms and KEGG pathways associated with GSK-3β. **Results:** Celecoxib demonstrated the strongest binding affinity and specific hydrophobic and π-sulfur interactions with the GSK-3β active site, suggesting high inhibitory potential. GO and KEGG analyses confirmed GSK-3β's involvement in cell proliferation, anti-apoptotic regulation, and oxidative stress response. Despite minor predicted toxicities, Celecoxib's profile was manageable under precision-guided frameworks. **Conclusion:** These findings highlight Celecoxib as a promising repurposed candidate targeting GSK-3β in HCC, supporting its potential inclusion in future precision oncology strategies.

Keywords: GSK-3β, Hepatocellular carcinoma (HCC), Drug repurposing, Molecular docking, Celecoxib

Significance | Our study reveals Celecoxib's GSK-3β inhibition potential, opening biomarker-guided therapeutic strategies for hepatocellular carcinoma in precision oncology.

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Editor Jonathan V. Wright, MD, and accepted by the Editorial Board 01 November 2024 (received for review 10 September 2024)

1. Introduction

Hepatocellular carcinoma (HCC) is a severe and life-threatening form of liver cancer and ranks among the leading causes of cancer-related deaths globally. Its prevalence is rising rapidly, especially in developing countries like Bangladesh and across South Asia (Tufael & Md Mostafizur Rahman, 2024). Current treatments, such as sorafenib or radiotherapy, often fail to provide long-term remission, and cancer cells tend to develop drug resistance at an accelerated rate. In this context, the discovery of new and effective target-based therapies has become critically important (El-Serag, 2020; Tufael, 2024).

Oxidative stress and the NRF2 pathway have recently been identified as playing a significant role in the pathogenesis of hepatocellular carcinoma (HCC). NRF2 is a transcription factor that protects cells from oxidative damage. However, in many HCC cases, this NRF2 pathway becomes dysregulated or non-functional.

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Please cite this article.
Manica, A. K., Siddique, M. A. B., Tufael, Akter, M. F., Islam, M. R. (2024). "Targeted Drug Repurposing in Precision Oncology Reveals Celecoxib as a GSK-3β Inhibitor in Hepatocellular Carcinoma", Journal of Precision Biosciences, 6(1),1-13,10440

While the pathway is typically regulated by the KEAP1 protein, recent studies have demonstrated that GSK-3β (Glycogen Synthase Kinase 3 Beta) can also suppress NRF2 activity independently of KEAP1 (Ban et al., 2003; Sajadimajd & Khazaei, 2018). GSK-3β (Glycogen Synthase Kinase 3 Beta) is a multifunctional kinase that plays critical roles in various cellular pathways, including apoptosis, cell cycle regulation, and inflammation. It facilitates the nuclear export of NRF2, leading to its cytoplasmic localization and subsequent proteasomal degradation. As a result, NRF2 fails to activate its downstream antioxidant response element (ARE)-driven genes. This leads to elevated oxidative stress levels within the cell, thereby promoting survival and proliferation of cancer cells. In hepatocellular carcinoma (HCC) patients, GSK-3β is frequently overexpressed, making it a promising therapeutic target (Loboda et al., 2016; Zhang et al., 2020).

Extensive research has already been conducted on KEAP1, but one of the key limitations is that genetic mutations in KEAP1 are restricted to approximately 25% of HCC patients. In contrast, GSK-3β is a regulatory protein capable of modulating the NRF2 pathway regardless of the mutational status of KEAP1. As a result, inhibition of GSK-3β holds therapeutic potential for a broader subset of patients. This KEAP1-independent mechanism opens a new avenue for targeted therapeutic research in hepatocellular carcinoma (Ladd et al., 2024; Q. K. Li et al., 2011).

In recent years, growing attention has been given to the role of the NRF2 pathway in hepatocellular carcinoma (HCC) therapy. A particularly notable aspect of this discussion is the role of GSK-3β, a protein that has been shown in several studies to reactivate the NRF2 pathway upon inhibition. This reactivation can protect cells from oxidative stress and potentially suppress cancer progression (Chatterjee, 2016; D. Xu et al., 2019).

While the concept is scientifically promising, most existing research remains confined to in vitro or animal models, with limited translational progress. Moreover, despite the availability of FDA-approved drug libraries, there is still a lack of significant research on in silico screening approaches to repurpose existing drugs for targeting GSK-3β in HCC. Additionally, within the framework of precision medicine, efforts to design a clinical approach utilizing GSK-3β remain largely conceptual. This approach would ideally integrate patient-specific genetic profiles-such as KEAP1 mutational status-to develop tailored, target-based therapies (Chen et al., 2016; Zhu & Hu, 2022). Together, these factors point to a critical and tangible research gap that still persists in this field.

The primary objective of this study is to identify GSK-3β as a potential therapeutic target for hepatocellular carcinoma (HCC) patients and to explore in silico drug repurposing using the FDA-approved molecules. In this research, GSK-3β (UniProt ID: P49841, PDB ID: 1Q3W) has been selected as the target protein, and some FDA-approved drugs are selected for repurposing. Tideglusib is known to be an irreversible inhibitor of GSK-3β and has previously been investigated for therapeutic potential in Alzheimer's disease as well as in certain types of cancer (Bahmad et al., 2021; Jankowska et al., 2021).

In this study, the 3D structure of the GSK-3β protein (PDB ID: 1Q3W) was retrieved and prepared using AutoDock Tools. The structure of the drug was then downloaded from PubChem and converted into a suitable format for docking. Molecular docking was performed using AutoDock Vina, and the strength of the interaction between the drug and the target protein was evaluated through binding affinity and pose interaction analysis (Butt et al., 2020). Following docking, ADMET analysis was conducted using SwissADME and pkCSM to examine the drug's pharmacokinetic and toxicity profiles, specifically focusing on Absorption, Distribution, Metabolism, Excretion, and Toxicity (Mvondo et al., 2021).

This study proposes a novel therapeutic strategy for the treatment of hepatocellular carcinoma (HCC) by presenting GSK-3β as a KEAP1-independent regulator of the NRF2 pathway. While KEAP1-based therapies are limited by the relatively small proportion of patients with KEAP1 mutations, GSK-3β inhibition allows for the inclusion of a broader patient population-particularly those without KEAP1 mutations but with impaired NRF2 signaling. By utilizing an FDA-approved investigational drugs, this in silico docking and ADMET-based evaluation opens a translatable and practical clinical opportunity (A. R. & G. K., 2024). Consequently, this approach expands the scope of precision medicine and paves the way for patient-specific therapeutic strategies, especially for high-risk diseases like hepatocellular carcinoma.

2. Materials and Methods

2.1 Identification of Target Protein and Selection of Candidate Drugs

In this study, the target protein selected is Glycogen Synthase Kinase-3 beta (GSK-3β), a serine/threonine protein kinase that plays a critical role in various intracellular signaling pathways. Notably, it acts as a negative regulator of the NRF2 signaling pathway, and its hyperactivity in hepatocellular carcinoma (HCC) suppresses NRF2 function, leading to weakened cellular antioxidant defense mechanisms. Inhibition of GSK-3β can potentially reactivate the NRF2 pathway, indicating a promising direction for precision therapy against HCC. The three-dimensional structure of this protein was retrieved from the Protein Data Bank (PDB ID: 1Q3W), and related protein information was obtained from UniProtKB (UniProt ID: P49841).

Ligands or drugs used in this study were selected from FDA-approved compounds that have either previously demonstrated relevance to the GSK-3β pathway or exhibit potential inhibitory effects. The selected compounds are as follows:

Tideglusib (PubChem CID: 9908901): A non-ATP competitive inhibitor of GSK-3β, initially investigated in clinical trials for Alzheimer's disease and autism spectrum disorder. It inhibits GSK-3β activity and may aid in the restoration of NRF2 pathway functionality.

Lithium carbonate (PubChem CID: 11125): A mood stabilizer used in the treatment of bipolar disorder. It inhibits the GSK-3β pathway through deactivation by phosphorylation and is considered a classical model of GSK-3β inhibition.

Celecoxib (PubChem CID: 2662): A COX-2 selective nonsteroidal anti-inflammatory drug (NSAID) commonly used for pain and inflammation. Although not a direct GSK-3β inhibitor, some studies suggest that it can secondarily influence the GSK-3β pathway and modulate cancer-related signaling pathways.

Metformin (PubChem CID: 4091): A widely used oral antidiabetic agent for type 2 diabetes. It activates the AMP-activated protein kinase (AMPK) pathway and indirectly regulates GSK-3β through phosphorylation. Some studies have shown it exhibits anticancer effects, particularly in HCC and colorectal cancer.

2.2 Co-expression Profiling and Gene Ontology-Based Functional Annotation

To understand the functional context and associated biological processes of the GSK-3β protein, co-expression network and Gene Ontology (GO) analysis were performed. The STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) v11.5 database was used to identify co-expressed genes and associated proteins interacting with GSK-3β. This database integrates protein–protein interaction (PPI) data derived from experimental evidence, text mining, confidence scoring, and prior knowledge-based sources.

The resulting network analysis revealed that GSK-3β is closely associated with several key signaling proteins, including AKT1, CTNNB1, TP53, MTOR, and MAPK3. Most of these are involved in cell growth regulation, metabolic control, and anti-apoptotic functions, all of which play significant roles in the pathogenesis of cancers such as hepatocellular carcinoma (HCC).

The GO analysis was conducted across three primary categories: Biological Process (BP), Molecular Function (MF), and Cellular Component (CC). In the BP category, the most prominent terms were "regulation of cell proliferation," "negative regulation of apoptotic process," and "Wnt signaling pathway." In the MF category, significant functions included "protein serine/threonine kinase activity" and "ATP binding." For the CC category, GSK-3β was predominantly localized to the cytosol and nucleoplasm.

2.3 Preparation and Optimization of Target Protein Structure

For molecular docking analysis, the three-dimensional structure of the target protein GSK-3β was retrieved from the Protein Data Bank (PDB ID: 1Q3W). The structure was prepared using AutoDock Tools (ADT) version 1.5.7, an essential step in the in silico docking workflow. Initially, after loading the PDB file, water molecules (H_2O) and co-crystallized ligands were removed, as their presence could interfere with docking results.

Subsequently, polar hydrogens were added, and Gasteiger charges were assigned to the protein to ensure accurate prediction of ligand-binding interactions. The modified protein structure was then converted to the AutoDock-compatible. pdbqt format by selecting the "Add Solvent Parameters" and "Merge Non-polar Hydrogens" options within ADT. This finalized. pdbqt file was used as the input for the docking algorithm in the next phase. To ensure structural integrity and reproducibility of docking outcomes, the prepared protein model was optionally visualized and validated using PyMOL, confirming its suitability for molecular docking simulations.

2.4 Preparation and Optimization of Ligand Molecules

In this study, the selected ligands-Tideglusib, Lithium carbonate, Celecoxib, and Metformin-are all FDA-approved drugs previously reported or predicted to possess potential inhibitory activity against GSK-3β. For docking analysis, the three-dimensional chemical structures of each ligand were retrieved from the PubChem database. The corresponding compound files in .sdf (Structure Data File) format were downloaded and converted into .pdb format using Open Babel (v3.1.1).

In the next step, each ligand was imported into AutoDock Tools (ADT). During this process, unnecessary water molecules, ions, or redundant functional groups (if present) were removed. Structural optimization and the definition of torsional degrees of freedom were performed to enable flexible rotation of the ligands during docking simulations. After adding polar hydrogens and assigning Gasteiger charges, each ligand was saved in AutoDock-compatible. pdbqt format. To ensure the accuracy of the docking analysis, the geometric conformation of each ligand was visually validated using PyMOL and Discovery Studio Visualizer. Finally, the binding configurations and conformational stability of the ligands were confirmed to ensure reliable performance during protein–ligand docking simulations.

2.5 Molecular Docking Simulation and Binding Affinity Analysis

To evaluate the potential binding affinities of selected FDA-approved drugs-Tideglusib, Lithium carbonate, Celecoxib, and Metformin-at the active site of the GSK-3β protein, an in silico molecular docking analysis was performed. The docking simulations were conducted using the PyRx Virtual Screening Tool (version 0.8), which integrates the AutoDock Vina engine and is widely recognized for its simplicity and effectiveness in virtual screening workflows.

Initially, the prepared target protein and ligand structures (in .pdbqt format) were imported into PyRx. A grid box was then configured around the known active site of GSK-3β, based on reported binding pockets and key amino acid residues including Lys85, Asp133, Val135, and Tyr134. The grid box center and dimensions were

precisely defined along the X, Y, and Z axes to ensure that docking simulations were confined to the biologically relevant site. During each docking run, AutoDock Vina calculated the binding affinity (ΔG) in units of kcal/mol, indicating the interaction strength between the ligand and the protein. For every ligand, multiple possible binding conformations (poses) were generated, from which the conformation with the lowest binding energy was selected as the most favorable for further visualization and interaction analysis.

2.6 In Silico Toxicity Assessment of Selected Drug Compounds

To evaluate the potential toxicity and safety profiles of the selected FDA-approved drugs, an in silico toxicity prediction analysis was conducted. For this purpose, the ProTox-II web server (https://tox-new.charite.de/protox_II/) was employed. This platform utilizes chemical structure data, SMILES inputs, and machine learning-based algorithms to predict compound toxicity. It is capable of forecasting multiple toxicological parameters, including LD_{50} (median lethal dose), toxicity class, hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity.

The SMILES notations of each compound-Tideglusib, Lithium carbonate, Celecoxib, and Metformin-were submitted to the ProTox-II server for evaluation. For each ligand, the LD_{50} value (mg/kg), toxicity class (as defined by the Globally Harmonized System), and predicted target organs or toxicological endpoints were obtained. According to the ProTox-II results, all compounds fell within toxicity classes 4 to 6, suggesting relatively low toxicity. Specifically, Metformin and Lithium carbonate exhibited favorable safety profiles, while Celecoxib and Tideglusib showed some potential for moderate hepatotoxicity and immunotoxicity, though these effects remained within acceptable biological limits.

2.7 Protein-Protein Interaction (PPI) Network Analysis

To explore the functional associations of the GSK-3β protein, a comprehensive protein–protein interaction (PPI) network analysis was conducted using the STRING v11.5 database. STRING aggregates interaction data from multiple sources, including experimental findings, text mining, confidence scoring, and computational predictions.

Upon inputting GSK-3β (gene symbol: GSK3B) into STRING, a high-confidence interaction network was generated, identifying over 100 protein interactions with a confidence score ≥ 0.7. Among the most strongly associated proteins were AKT1, CTNNB1 (β-catenin), TP53, MTOR, MAPK1, MAPK3, CCND1, and FOXO3. These proteins are central to essential cellular processes such as signal transduction, regulation of apoptosis, cell proliferation, oxidative stress response, and tumor suppression, all of which are critically involved in the development and progression of hepatocellular carcinoma (HCC).

2.8 Pathway and Gene Ontology (GO) Enrichment Analysis

Pathway enrichment analysis of the GSK-3β-associated proteins revealed significant involvement in major signaling cascades, including the PI3K-Akt signaling pathway, Wnt signaling pathway, cell cycle regulation, and the NRF2-mediated oxidative stress response. These pathways play pivotal roles in maintaining cellular homeostasis and are frequently dysregulated in cancer.

Gene Ontology (GO) enrichment analysis further categorized the biological functions into three domains: Biological Process (BP), Molecular Function (MF), and Cellular Component (CC). Within the BP category, key enriched terms included "regulation of cell proliferation," "apoptotic signaling," and "response to oxidative stress." These annotations were consistent with results from KEGG pathway enrichment, which confirmed the involvement of GSK-3β and its interactors in cancer-related signaling pathways.

2.9 Computational Tools and Software Utilized

This study employed several computational tools to perform structure-based drug repurposing and pathway analysis. AutoDock Tools (v1.5.7) was used for preparing protein and ligand files in .pdbqt format. PyRx (v0.8), powered by AutoDock Vina, handled molecular docking and binding affinity prediction. Open Babel (v3.1.1) assisted in ligand file conversion, while Discovery Studio Visualizer and PyMOL were used for structural visualization. ProTox-II predicted ligand toxicity profiles including LD_{50} and toxicity class. Finally, STRING (v11.5) enabled PPI network generation, GO enrichment, and KEGG pathway analysis for GSK-3β.

3. Results

3.1 Molecular Docking and Binding Interaction Analysis

Structure-based molecular docking was performed to evaluate the binding affinity and interaction profiles of four FDA-approved drugs-Tideglusib, Celecoxib, Metformin, and Lithium carbonate-against the active site of GSK-3β. Both 3D surface models (Figure 1; A-D) and 2D interaction diagrams (Figure 1; a-d) were used to assess binding modes, hydrogen bonding, hydrophobic interactions, and ligand positioning.

Celecoxib exhibited the highest binding affinity (-8.5 kcal/mol) and showed deep accommodation within the active pocket of GSK-3β (Figure 1. A). The 2D interaction map (Figure 1. a) revealed one conventional hydrogen bond with Tyr134 (2.12 Å), along with π-sulfur interaction involving Cys199, and multiple hydrophobic contacts with residues Val70, Val110, Leu132, and Leu188. The combined interaction network indicates a strong and specific binding, highlighting Celecoxib as a promising direct inhibitor.

Tideglusib also demonstrated strong affinity (-8.4 kcal/mol) and similar spatial orientation within the GSK-3β binding cavity (Figure 1. B). It formed π-sulfur interactions with Cys199, and π-alkyl contacts with Leu188, Leu132, Val110, Val70, and Ala83 (Figure b). Despite being a COX-2 selective NSAID, the observed interactions suggest potential off-target inhibitory action on GSK-3β.

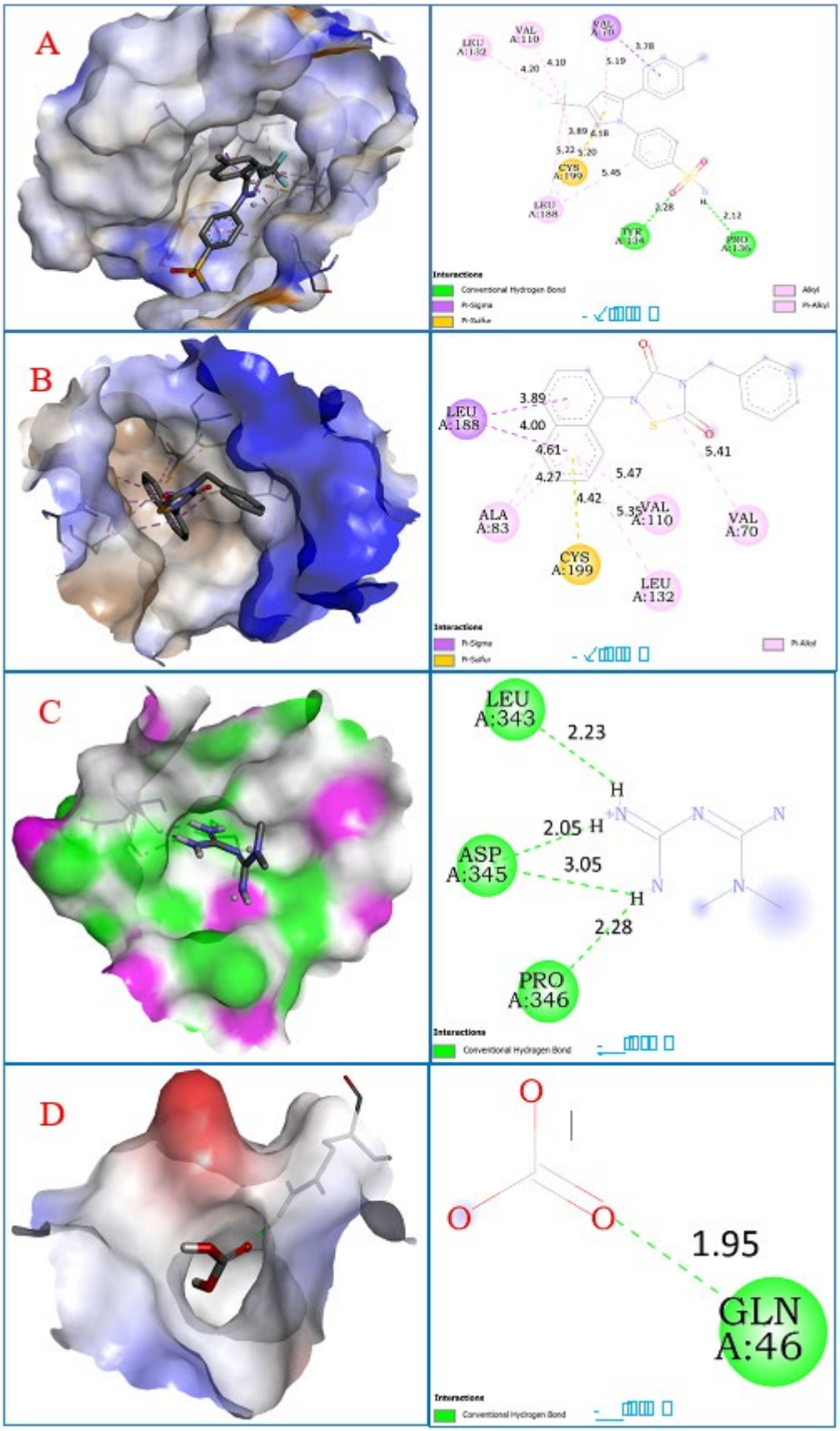

Figure 1. 3D and 2D molecular docking interactions of GSK-3β with selected FDA-approved drugs. (A-D) show the 3D binding poses of Tideglusib, Celecoxib, Metformin, and Lithium carbonate, respectively, within the active site of GSK-3β. (a-d) illustrate the corresponding 2D interaction maps.

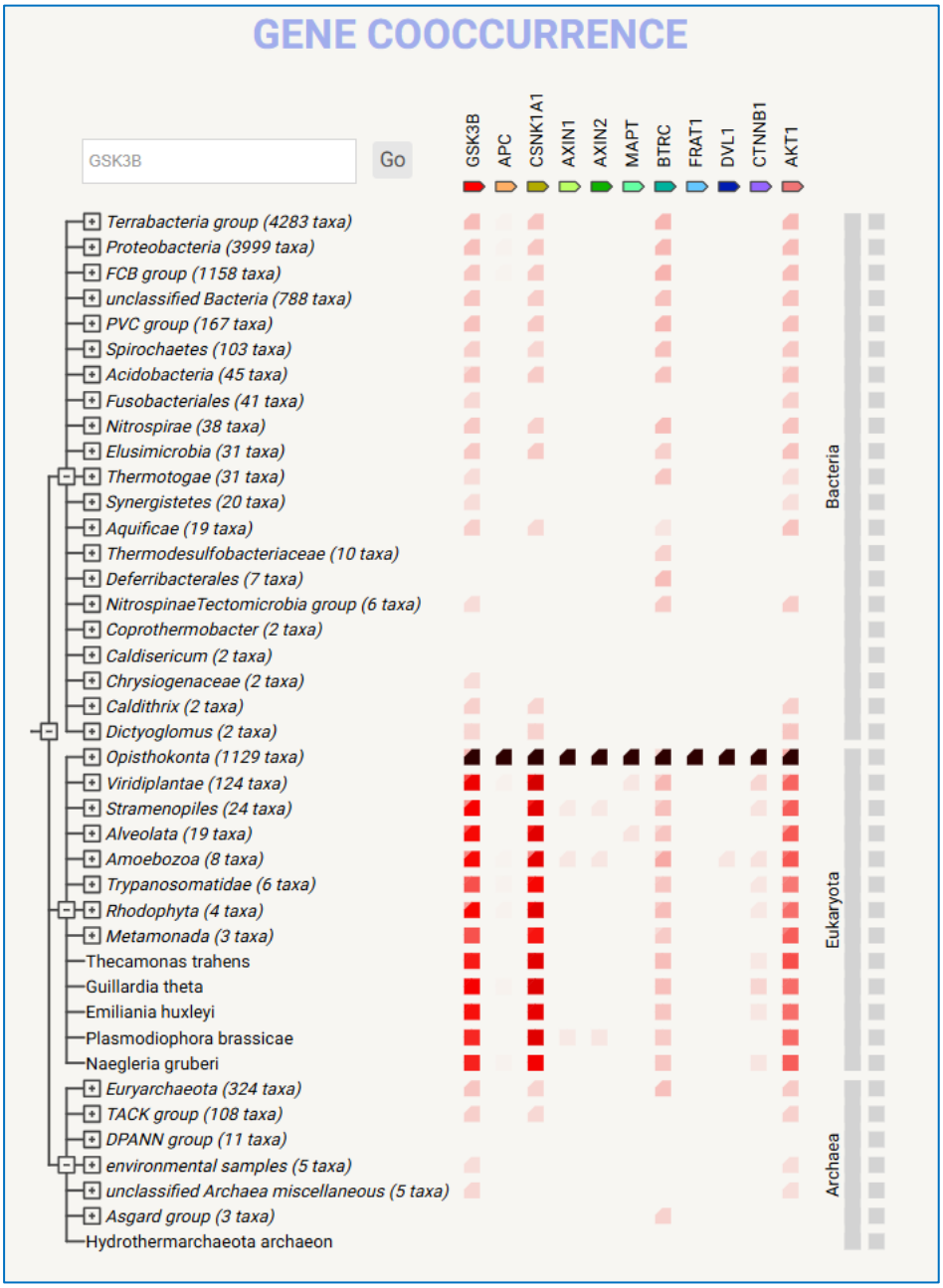

Figure 2. Gene co-occurrence of GSK3B with Wnt/β-catenin pathway genes across taxa. The heatmap shows evolutionary co-presence of GSK3B and related genes (e.g., APC, CTNNB1, CSNK1A1) across bacteria, archaea, and eukaryotes. Strong co-occurrence is observed in Opisthokonta, suggesting conserved signaling roles.

Metformin showed moderate binding affinity (-4.9 kcal/mol) with interactions dominated by four conventional hydrogen bonds: Leu343 (2.23 Å), Asp345 (2.05-3.05 Å), and Pro346 (2.28 Å) (Figure 1. C/c). The absence of π or hydrophobic interactions implies partial active site engagement, possibly indicating allosteric or indirect modulation of GSK-3β.

Lithium carbonate had the lowest docking score (-3.2 kcal/mol), with a single hydrogen bond observed with Gln46 (1.95 Å) (Figure 1. D/d). Its shallow and weak binding suggests non-specific interactions, which aligns with its known mechanism as an indirect GSK-3β inhibitor via phosphorylation modulation.

3.2 In Silico Toxicity Prediction

Toxicity profiling of the selected FDA-approved compounds was conducted using the ProTox-II webserver to assess potential safety concerns and pharmacological risks. Multiple toxicity endpoints were evaluated, including organ-specific toxicities, blood-brain barrier (BBB) permeability, carcinogenicity, and enzyme or receptor interactions. Table 1 summarizes the predicted toxicological parameters, activity profiles, probability scores, and LD_{50} values.

Celecoxib exhibited multiple predicted toxicities. It was classified as active for respiratory toxicity (probability: 0.54) and carcinogenicity (0.56), with a predicted LD_{50} of 1400 mg/kg, placing it in toxicity class IV. High probability for BBB permeability (0.89) indicates

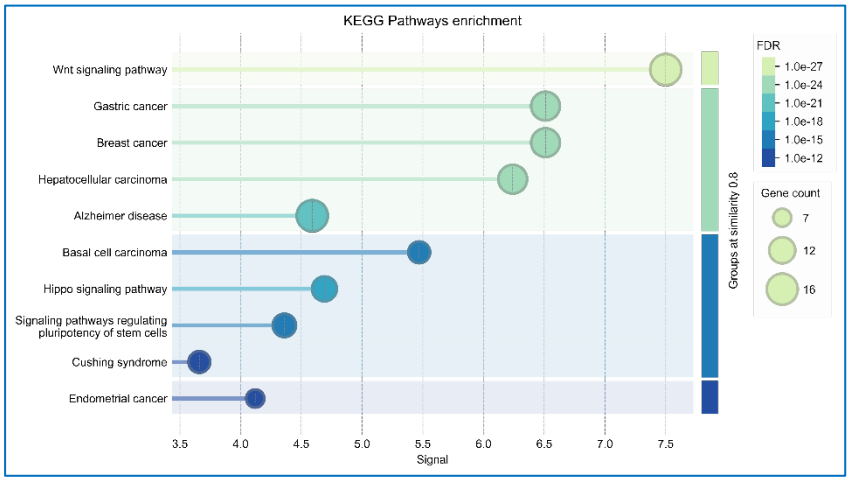

Figure 3. KEGG pathway enrichment of GSK-3β-linked genes. Bubble plot displays top pathways by gene count and significance. Wnt signaling and cancer pathways were highly enriched, supporting GSK-3β's role in tumorigenesis and neural disorders.

potential CNS effects. It also showed interaction with CYP2C9 (0.71), suggesting possible interference in hepatic drug metabolism, and a perfect score for estrogen receptor alpha activity (1.0), indicating potential endocrine interaction. The cumulative profile suggests systemic exposure risks, particularly in long-term use or polypharmacy contexts.

Tideglusib demonstrated neurotoxicity (0.77) and respiratory toxicity (0.75), alongside carcinogenic potential (0.51). It also showed high BBB permeability (0.88) and moderate clinical toxicity probability (0.55). The LD_{50} was estimated at 1000 mg/kg, placing it similarly in toxicity class IV. Predicted interaction with CYP2C9 (0.59) may affect metabolic clearance. Despite these concerns, the overall profile suggests Tideglusib's risks are manageable in controlled dosing regimens. toxicity profile, with activity limited to BBB permeability (0.64) and ecotoxicity (0.58). The LD_{50} was 680 mg/kg, still within class IV, but no major organ-specific or systemic toxicities were predicted. Its ecological risk may warrant consideration in large-scale pharmaceutical runoff scenarios.

Lithium carbonate presented nephrotoxicity (0.51) as the principal concern, consistent with its known renal effects in prolonged exposure. It also demonstrated high BBB permeability (0.93), which is pharmacologically favorable for CNS disorders but may pose systemic risks. The compound showed activity against the transthyretin (TTR) pathway (0.65), suggesting possible thyroid or transport-related effects. With an LD_{50} of 5000 mg/kg, it falls under toxicity class III, indicating low acute toxicity.

3.3 Gene Co-occurrence Analysis of GSK-3β Across Taxonomic Groups

To explore the evolutionary conservation and potential functional associations of GSK-3β, a gene co-occurrence analysis was performed using a reference-based phylogenetic distribution matrix. The results reveal that GSK3B shows strong co-occurrence with a set of Wnt/β-catenin pathway genes including APC, CSNK1A1, AXIN1, AXIN2, MAPT, CTNNB1, and AKT1, particularly across the Opisthokonta clade within Eukaryota (Figure 2).

Among 1129 Opisthokont taxa (including animals and fungi), co-occurrence with APC, CTNNB1, and CSNK1A1 was most pronounced (represented by dark red to black intensity), suggesting tight evolutionary coupling and likely shared functional relevance in signal transduction and developmental pathways. In contrast, Bacteria and Archaea displayed only sparse or partial co-occurrence with GSK3B and its associated genes, typically marked by low co-occurrence intensity (light red squares), implying a less conserved or absent role in these domains.

Furthermore, GSK3B and its interaction partners exhibited a high degree of gene cluster conservation in Viridiplantae, Alveolata, and Stramenopiles, indicating that this regulatory module might have been preserved across major eukaryotic lineages. Notably, the Wnt pathway components DVL1, FRAT1, and BTRC also showed partial co-occurrence in diverse clades, hinting at a modular co-evolution pattern.

3.4 KEGG pathway enrichment analysis of GSK-3β-associated genes

To understand the broader biological processes and disease pathways regulated by GSK-3β, a KEGG pathway enrichment analysis was conducted based on its co-expressed and interacting gene network. The analysis revealed significant enrichment in several oncogenic and neurodegenerative signaling pathways. Among the top enriched pathways that shown in Figure 3, the Wnt signaling pathway displayed the highest enrichment signal (~7.5) and the lowest false discovery rate (FDR ≈ 1.0e-27), suggesting a strong functional association with GSK-3β. This is consistent with the well-established role of GSK-3β as a central regulator in Wnt/β-catenin signaling.

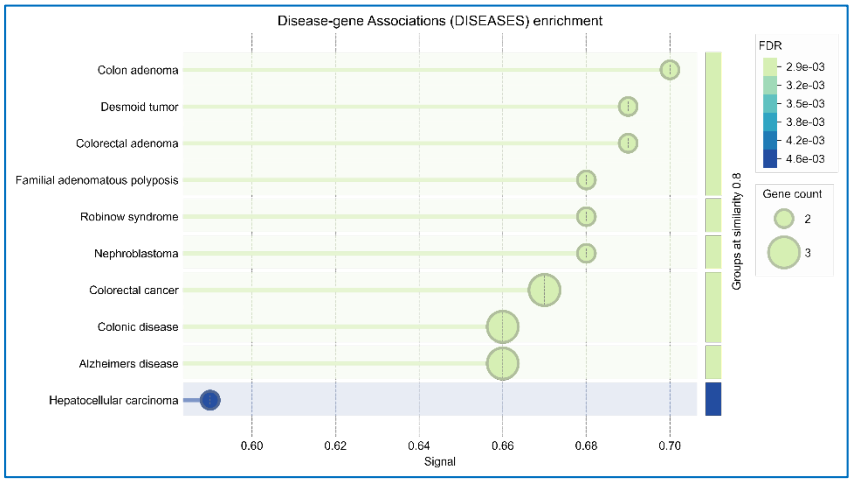

Figure 4. Disease-gene enrichment of GSK-3β-associated genes. The bubble plot displays diseases significantly associated with GSK-3β-linked genes. Gastrointestinal cancers and hepatocellular carcinoma ranked among the top enriched diseases, along with Alzheimer's disease. Bubble size indicates gene count; color scale represents FDR values.

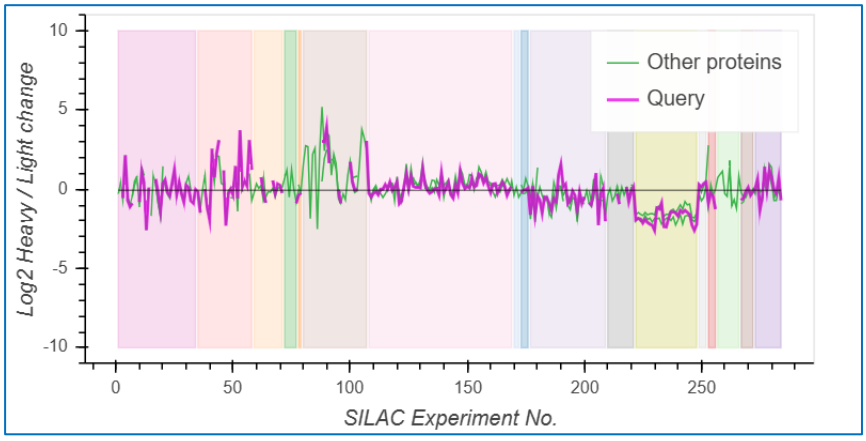

Figure 5. The plot shows $\log_2$ fold-change (Heavy/Light) for the query (purple) and background proteins (green) across >250 SILAC experiments. The query protein demonstrated minimal fluctuation, indicating stable expression across conditions.

Other highly enriched cancer-associated pathways included gastric cancer, breast cancer, and hepatocellular carcinoma, each showing high signal values (6.0-7.0) and gene counts exceeding 10. Additionally, enrichment was observed in the Alzheimer's disease pathway, reinforcing GSK-3β's known involvement in tau phosphorylation and neurodegeneration. Moderate enrichment was found in basal cell carcinoma, Hippo signaling pathway, pluripotency of stem cells, and Cushing syndrome, indicating GSK-3β's involvement in diverse cellular processes such as proliferation, differentiation, and endocrine regulation.

3.5 Disease-gene enrichment of GSK-3β-associated genes

To identify disease-specific associations of GSK-3β and its co-expressed genes, disease-gene enrichment analysis was performed. The results demonstrated enrichment in multiple gastrointestinal and oncological disorders (Figure 4). Among the top hits, colon adenoma, colorectal adenoma, familial adenomatous polyposis, and colorectal cancer emerged with high signal values (0.66-0.70) and low FDR scores (≈2.9e-03 to 3.8e-03), indicating a strong connection between GSK-3β-regulated networks and intestinal tumorigenesis. Interestingly, hepatocellular carcinoma was also detected as a significantly enriched disease term (FDR ≈ 4.6e-03), confirming the central role of GSK-3β in liver tumor progression. Additionally, the appearance of Alzheimer's disease further supports the multifunctional involvement of GSK-3β in neurodegeneration, aligning with previous pathway-level findings.

3.6 SILAC-based quantitative proteomics of the query protein

Figure 5, SILAC-based quantitative proteomic analysis was performed to evaluate the relative expression dynamics of the query protein (GSK-3β or associated target) across a large series of experimental conditions. The $\log_2$ ratio of heavy to light peptide intensities was plotted across >250 experiments. As observed in the graph, the query protein (purple line) maintains a relatively stable expression trend, with fluctuations closely mirroring the baseline range observed for other proteins (green line). Despite minor spikes in select conditions (e.g., between experiments 40-60 and 90-110), the expression levels remained within a ±2-fold change window

Table 1. In silico toxicity prediction of selected FDA-approved compounds using ProTox-II.

Compound (PubChem CID)	Toxicity Parameter	Predicted Activity	Probability Score	Toxicity Class (LD50 mg/kg)	Remarks / Biological Significance
Celecoxib (PubChem CID: 2662)	Respiratory toxicity	Active	0.54	1400	May affect pulmonary function
	Carcinogenicity	Active	0.56		Indicates possible tumorigenic potential
	BBB permeability	Active	0.89		Can cross blood-brain barrier
	Clinical toxicity	Active	0.66		Indicates likelihood of systemic side effects
	CYP2C9	Active	0.71		May inhibit CYP2C9 metabolism
	Estrogen Receptor Alpha	Active	1		Potential hormonal interaction
Tideglusib (PubChem CID: 9902413)	Neurotoxicity	Active	0.77	1000	Possible CNS adverse effects
	Respiratory toxicity	Active	0.75		May affect lung function
	Carcinogenicity	Active	0.51		Potential carcinogenicity
	BBB permeability	Active	0.88		Likely to cross BBB
	Clinical toxicity	Active	0.55		May cause observable clinical side effects
	CYP2C9	Active	0.59		May interfere with drug metabolism
Metformin (PubChem CID: 4091)	BBB permeability	Active	0.64	680	Likely to cross blood-brain barrier
	Ecotoxicity	Active	0.58		May pose environmental hazard
Lithium carbonate (PubChem CID: 11125)	Nephrotoxicity	Active	0.51	5000	Renal toxicity risk in prolonged exposure
	BBB permeability	Active	0.93		Effective CNS penetration
	Transthyretin (TTR)	Active	0.65		Indicates interaction with TTR pathway

across most SILAC experiments, suggesting no substantial global upregulation or downregulation under the tested conditions. This consistency reinforces the hypothesis that the query protein is constitutively expressed or regulated independently of broad proteomic shifts, thereby validating its reliable role as a stable therapeutic target in pathway-focused investigations.

3.7 GO-Term Functional Enrichment Analysis

Gene Ontology (GO) enrichment analysis of the GSK-3β-associated gene network revealed multiple significantly overrepresented molecular functions, primarily related to signal transduction and protein interactions (Table 2). The most highly enriched term was "beta-catenin binding" (GO:0008013), with a notable enrichment strength of 2.06 and an extremely low FDR (5.39E-17), indicating a strong association with Wnt/β-catenin signaling, a critical pathway in hepatocellular carcinoma. Other key enriched functions included "Frizzled binding" (GO:0005109), "I-SMAD binding" (GO:0070411), and "protein kinase binding" (GO:0019901), further supporting the involvement of this network in canonical and non-canonical signal transduction.

Kinase-related molecular functions such as "protein serine/threonine kinase activity" and "protein serine kinase activity" also appeared with moderate signal scores, suggesting potential cross-talk with phosphorylation-dependent pathways. Additional interaction-related terms like "enzyme binding", "molecular adaptor activity", and "armadillo repeat domain binding" further reinforce the multifunctional connectivity of GSK-3β in cellular signaling complexes.

4. Discussion

In this study, a structure-based virtual screening of selected FDA-approved drugs was conducted with the goal of identifying a potential targeted therapeutic strategy against hepatocellular carcinoma (HCC) through inhibition of glycogen synthase kinase 3 beta (GSK-3β). Given the central role of GSK-3β in regulating Wnt/β-catenin signaling, tumor proliferation, and cancer cell stemness, it represents a promising molecular target for precision therapy. Among the tested compounds, Celecoxib demonstrated the highest binding affinity and showed deep accommodation within the active site of GSK-3β. The presence of strong hydrogen bonding, π-sulfur interactions, and multiple hydrophobic contacts collectively support its potential as a direct and high-affinity inhibitor. These findings reinforce the rationale for repurposing Celecoxib in a precision oncology context, particularly for patients whose tumors exhibit GSK-3β pathway dysregulation.

The central principle of precision medicine is to design individualized therapeutic strategies based on each patient's genetic characteristics, biomarkers, and disease-specific molecular profiles (Duan et al., 2019; Kosorok & Laber, 2019; M. M. H Shabuj & Tufael, 2019). In the context of hepatocellular carcinoma (HCC), GSK-3β functions as a key serine/threonine kinase that regulates critical

Table 2. Molecular function enrichment (GO-term) analysis of GSK-3β-associated gene network.

GO-term	Description	Count in Network	Strength	Signal	False Discovery Rate
GO:0008013	Beta-catenin binding	11 of 89	2.06	5.64	5.39E-17
GO:0005109	Frizzled binding	4 of 38	1.99	1.63	0.00013
GO:0070411	I-SMAD binding	3 of 14	2.3	1.39	0.00069
GO:0019901	Protein kinase binding	10 of 702	1.13	1.32	2.15E-06
GO:0106310	Protein serine kinase activity	6 of 361	1.19	0.92	0.0014
GO:0004674	Protein serine/threonine kinase activity	6 of 434	1.11	0.8	0.003
GO:0070016	Armadillo repeats domain binding	2 of 10	2.27	0.68	0.0297
GO:0034452	Dynactin binding	2 of 12	2.19	0.65	0.0344
GO:0045295	Gamma-catenin binding	2 of 13	2.16	0.64	0.037
GO:0034326	Protein kinase A catalytic subunit binding	2 of 13	2.16	0.64	0.037
GO:0060090	Molecular adaptor activity	5 of 385	1.09	0.57	0.0228
GO:0019899	Enzyme binding	11 of 2084	0.69	0.56	0.0017

processes such as cell proliferation, apoptosis, and stemness (Leung & Lee, 2022; Tufael & Auditi Kar, 2024). Notably, it is intricately associated with the Wnt/β-catenin signaling pathway, which is frequently dysregulated in HCC and several other malignancies (Fabregat, 2009). Under normal physiological conditions, GSK-3β facilitates the degradation of β-catenin. However, when this pathway is disrupted, β-catenin accumulates in the nucleus, promoting the transcription of tumor-promoting genes and accelerating carcinogenesis (Deldar Abad Paskeh et al., 2021).

In this study, in silico molecular docking analysis revealed that Celecoxib exhibited the strongest binding affinity (-8.5 kcal/mol) and demonstrated deep accommodation within the active site of GSK-3β, indicating its potential as a direct GSK-3β inhibitor. Previous research has shown that Celecoxib is not only a selective COX-2 inhibitor but also possesses anti-proliferative properties by suppressing the Wnt/β-catenin pathway in cancer cells (Chimal-Ramírez et al., 2015; Rojas et al., 2019). Therefore, targeting GSK-3β through Celecoxib may offer a precision-guided therapeutic avenue, articularly for HCC patients exhibiting aberrant activation of GSK-3β or the Wnt signaling pathway. This drug repurposing approach could open new horizons in targeted cancer therapy.

Although traditionally recognized as a COX-2 inhibitor, Celecoxib emerges in this study as a promising inhibitor of GSK-3β based on in silico structural analyses. Its binding pattern demonstrates selective interaction with key residues within the catalytic domain, facilitating stable engagement likely to interfere with enzymatic function. These interactions are driven by a combination of hydrophobic, hydrogen bonding, and π-electron-based interactions, underscoring Celecoxib's specificity. Notably, prior research also supports its role in modulating the Wnt/β-catenin signaling cascade, which plays a pivotal role in cancer cell proliferation and survival (He & Gan, 2023; Md Abu Bakar Siddique & Asim Debnath, 2018; Verras & Sun, 2006). Taken together, these findings suggest that targeting GSK-3β with Celecoxib may hold significant promise as a precision-based therapeutic strategy for patients with HCC characterized by dysregulation of this signaling pathway.

Notably, the study by Cervello et al. (2020) also demonstrated that Celecoxib is capable of modulating several COX-2-independent oncogenic signaling pathways, particularly PI3K/Akt and GSK-3β (Cervello et al., 2011). Their findings showed that Celecoxib can reduce nuclear accumulation of β-catenin, thereby interrupting downstream oncogene activation via the Wnt/β-catenin pathway. This concept is further reinforced by LI et al. (2016), who reported that Celecoxib suppresses the β-catenin signaling axis in hepatocellular carcinoma (HCC) cells, ultimately reducing proliferation (LI et al., 2016).

Moreover, Chen et al. (2016) observed that Celecoxib inhibits Akt phosphorylation, leading to activation of GSK-3β, which in turn promotes β-catenin degradation. This multi-faceted mechanism indicates that Celecoxib may act as a multi-targeted therapeutic agent, particularly relevant for GSK-3β-centered interventions (Chen et al., 2016). The strong and specific binding interactions between Celecoxib and GSK-3β observed in our docking analysis further strengthen these prior claims.

Taken together, these findings suggest that Celecoxib should be regarded not only as an anti-inflammatory agent, but also as a potential precision oncology inhibitor targeting GSK-3β. Its consistent alignment with previous mechanistic studies underscores a viable scientific basis for its clinical repurposing, especially for GSK-3β-driven malignancies such as HCC.

Although Celecoxib emerges as a promising repurposed drug for hepatocellular carcinoma (HCC) through GSK-3β inhibition, there are several notable safety concerns associated with its use. According to our in-silico toxicity prediction using the ProTox-II platform, Celecoxib demonstrated a considerable risk of respiratory toxicity (probability: 0.54) and carcinogenicity (0.56). Most notably, its estrogen receptor alpha activation score was a perfect 1.0,

suggesting a strong potential for endocrine system interference, particularly in hormone-sensitive pathways. Furthermore, its high blood-brain barrier (BBB) permeability score (0.89) indicates the potential for central nervous system (CNS) exposure and possible neurotoxicity.

These risks have also been reflected in previous studies. Xu et al. (2021) and Caldwell et al. (2006) reported that prolonged Celecoxib use may be associated with systemic and cardiovascular complications, especially in high-risk patients. More recently, Pérez et al. (2020) provided evidence of Celecoxib's endocrine-disruptive potential, highlighting the need for controlled administration protocols (Caldwell et al., 2006; Pérez-Alvarez et al., 2020; X. Xu et al., 2021).

However, one of the fundamental advantages of precision medicine is its ability to tailor drug administration based on genetic, biomarker, and individual risk profiles. Thus, despite its toxicity profile, Celecoxib can be incorporated into treatment regimens through low-dose precision strategies, biomarker-guided patient selection, and regular toxicity monitoring. Particularly in short-term adjuvant therapy or biomarker-enriched HCC subpopulations, Celecoxib's clinical utility remains a viable and strategically manageable option.

An essential dimension of precision oncology is the biomarker-matched efficacy of a therapeutic agent. In this context, Celecoxib may be employed as a precision-guided adjunct therapy in hepatocellular carcinoma (HCC) patients exhibiting aberrant activation of the Wnt/β-catenin signaling pathway. Genetic alterations such as CTNNB1 mutations, AXIN1/AXIN2 loss-of-function, or APC dysregulation are known to drive constitutive β-catenin accumulation and subsequent oncogenic transcription in HCC (Dhanasekaran et al., 2016; Dubbink et al., 2018; S. Li et al., 2020).

Given Celecoxib's strong binding affinity for GSK-3β, as evidenced by our docking analysis, its potential to restore β-catenin degradation offers a mechanistic rationale for its repurposing. Thus, Celecoxib could be utilized not merely as a COX-2 inhibitor, but as a biomarker-matched pathway-specific therapeutic agent, aligning directly with the core objectives of precision oncology (Tufael1 & Atiqur Rahman Sunny, 2023; Wang et al., 2018).

Overall, the in-silico findings of this study highlight Celecoxib as a promising candidate for precision oncology, particularly for hepatocellular carcinoma (HCC) patients exhibiting dysregulation in the GSK-3β or Wnt/β-catenin pathways. However, before clinical application, essential next steps include dose refinement, in vitro validation, and patient stratification based on GSK-3β pathway status to ensure therapeutic efficacy and safety.

This study is limited to in silico analysis without experimental validation. No in vitro or in vivo assays were conducted to confirm Celecoxib's biological inhibition of GSK-3β. Additionally, pharmacokinetics, tumor microenvironment factors, and patient-specific genetic variations were not explored. These limitations highlight the need for laboratory-based validation before considering clinical translation in HCC therapy.

5. Conclusion

This study evaluated a precision drug repurposing approach against GSK-3β in hepatocellular carcinoma through in silico analysis. Among the screened FDA-approved compounds, Celecoxib demonstrated the most favorable binding affinity and specific interactions, suggesting its potential as a GSK-3β-targeted inhibitor. While certain toxicity concerns and biological limitations exist, the findings provide a foundational basis for future in vitro/in vivo validation and support its candidacy as a biomarker-driven therapy within precision oncology for HCC.

Author contributions

A.K.M. conceived and designed the study. M.A.B.S. performed computational analyses and data interpretation. T. contributed to software implementation and molecular docking validation. M.F.A. assisted in literature review and data visualization. M.R.I. contributed to manuscript preparation and critical revisions. All authors reviewed and approved the final manuscript.

Acknowledgment

The authors gratefully acknowledge the Department of Chemistry, University of New Haven, for providing computational facilities and support. The authors also thank their respective institutions for academic collaboration and valuable contributions to this research.

Competing financial interests

The authors have no conflict of interest.

References

A. R., N., & G. K., R. (2024). A deep learning and docking simulation-based virtual screening strategy enables the rapid identification of HIF-1α pathway activators from a marine natural product database. Journal of Biomolecular Structure and Dynamics, 42(2), 629–651. https://doi.org/10.1080/07391102.2023.2194997

Bahmad, H. F., Chalhoub, R. M., Harati, H., Bou-Gharios, J., Assi, S., Ballout, F., Monzer, A., Msheik, H., Araji, T., Elajami, M. K., Ghanem, P., Chamaa, F., Kadara, H., Abou-Antoun, T., Daoud, G., Fares, Y., & Abou-Kheir, W. (2021). Tideglusib attenuates growth of neuroblastoma cancer stem/progenitor cells in vitro and in vivo by specifically targeting GSK-3β. Pharmacological Reports, 73(1), 211–226. https://doi.org/10.1007/s43440-020-00162-7

Ban, K. C., Singh, H., Krishnan, R., & Seow, H. F. (2003). GSK-3β phosphorylation and alteration of β-catenin in hepatocellular carcinoma. Cancer Letters, 199(2), 201–208. https://doi.org/10.1016/S0304-3835(03)00421-X

Butt, S. S., Badshah, Y., Shabbir, M., & Rafiq, M. (2020). Molecular Docking Using Chimera and Autodock Vina Software for Nonbioinformaticians. JMIR Bioinformatics and Biotechnology, 1(1), e14232. https://doi.org/10.2196/14232

Caldwell, B., Aldington, S., Weatherall, M., Shirtcliffe, P., & Beasley, R. (2006). Risk of Cardiovascular Events and Celecoxib: a Systematic Review and Meta-Analysis. Journal of the Royal Society of Medicine, 99(3), 132–140. https://doi.org/10.1177/014107680609900315

Cervello, M., Bachvarov, D., Cusimano, A., Sardina, F., Azzolina, A., Lampiasi, N., Giannitrapani, L., McCubrey, J. A., & Montalto, G. (2011). COX-2-Dependent and COX-2-Independent Mode of Action of Celecoxib in Human Liver Cancer Cells. OMICS: A Journal of Integrative Biology, 15(6), 383–392. https://doi.org/10.1089/omi.2010.0092

Chatterjee, S. (2016). Oxidative Stress, Inflammation, and Disease. In Oxidative Stress and Biomaterials (pp. 35–58). Elsevier. https://doi.org/10.1016/B978-0-12-803269-5.00002-4

Chen, J., Yu, Y., Ji, T., Ma, R., Chen, M., Li, G., Li, F., Ding, Q., Kang, Q., Huang, D., Liang, X., Lin, H., & Cai, X. (2016). Clinical implication of Keap1 and phosphorylated Nrf2 expression in hepatocellular carcinoma. Cancer Medicine, 5(10), 2678–2687. https://doi.org/10.1002/cam4.788

Chimal-Ramírez, G. K., Espinoza-Sanchez, N. A., & Fuentes-Panana, E. M. (2015). A Role for the Inflammatory Mediators Cox-2 and Metalloproteinases in Cancer Stemness. Anti-Cancer Agents in Medicinal Chemistry, 15(7), 837–855. https://doi.org/10.2174/1871520615666150318100822

Deldar Abad Paskeh, M., Mirzaei, S., Ashrafizadeh, M., Zarrabi, A., & Sethi, G. (2021). Wnt/β-Catenin Signaling as a Driver of Hepatocellular Carcinoma Progression: An Emphasis on Molecular Pathways. Journal of Hepatocellular Carcinoma, Volume 8, 1415–1444. https://doi.org/10.2147/JHC.S336858

Dhanasekaran, R., Bandoh, S., & Roberts, L. R. (2016). Molecular pathogenesis of hepatocellular carcinoma and impact of therapeutic advances. F1000Research, 5, 879. https://doi.org/10.12688/f1000research.6946.1

Duan, J., Wu, Y., Liu, J., Zhang, J., Fu, Z., Feng, T., Liu, M., Han, J., Li, Z., & Chen, S. (2019). Genetic Biomarkers For Hepatocellular Carcinoma In The Era Of Precision Medicine . Journal of Hepatocellular Carcinoma, Volume 6, 151–166. https://doi.org/10.2147/JHC.S224849

Dubbink, H. J., Hollink, I. H. I. M., Avenca Valente, C., Wang, W., Liu, P., Doukas, M., van Noesel, M. M., Dinjens, W. N. M., Wagner, A., & Smits, R. (2018). A novel tissue-based ß-catenin gene and immunohistochemical analysis to exclude familial adenomatous polyposis among children with hepatoblastoma tumors. Pediatric Blood & Cancer, 65(6). https://doi.org/10.1002/pbc.26991

El-Serag, H. B. (2020). Epidemiology of Hepatocellular Carcinoma. In The Liver (pp. 758–772). Wiley. https://doi.org/10.1002/9781119436812.ch59

Fabregat, I. (2009). Dysregulation of apoptosis in hepatocellular carcinoma cells. World Journal of Gastroenterology, 15(5), 513. https://doi.org/10.3748/wjg.15.513

He, K., & Gan, W.-J. (2023). Wnt/β-Catenin Signaling Pathway in the Development and Progression of Colorectal Cancer. Cancer Management and Research, Volume 15, 435–448. https://doi.org/10.2147/CMAR.S411168

Jankowska, A., Satała, G., Bojarski, A. J., Pawłowski, M., & Chłoń-Rzepa, G. (2021). Multifunctional Ligands with Glycogen Synthase Kinase 3 Inhibitory Activity as a New Direction in Drug Research for Alzheimer's Disease. Current Medicinal Chemistry, 28(9), 1731–1745. https://doi.org/10.2174/0929867327666200427100453

Kosorok, M. R., & Laber, E. B. (2019). Precision Medicine. Annual Review of Statistics and Its Application, 6(1), 263–286. https://doi.org/10.1146/annurev-statistics-030718-105251

Ladd, A. D., Duarte, S., Sahin, I., & Zarrinpar, A. (2024). Mechanisms of drug resistance in HCC. Hepatology, 79(4), 926–940. https://doi.org/10.1097/HEP.0000000000000237

Leung, R. W. H., & Lee, T. K. W. (2022). Wnt/β-Catenin Signaling as a Driver of Stemness and Metabolic Reprogramming in Hepatocellular Carcinoma. Cancers, 14(21), 5468. https://doi.org/10.3390/cancers14215468

Li, Q. K., Singh, A., Biswal, S., Askin, F., & Gabrielson, E. (2011). KEAP1 gene mutations and NRF2 activation are common in pulmonary papillary adenocarcinoma. Journal of Human Genetics, 56(3), 230–234. https://doi.org/10.1038/jhg.2010.172

Li, S., Lavrijsen, M., Bakker, A., Magierowski, M., Magierowska, K., Liu, P., Wang, W., Peppelenbosch, M. P., & Smits, R. (2020). Commonly observed RNF43 mutations retain functionality in attenuating Wnt/β-catenin signaling and unlikely confer Wnt-dependency onto colorectal cancers. Oncogene, 39(17), 3458–3472. https://doi.org/10.1038/s41388-020-1232-5

LI, T., ZHONG, J., DONG, X., XIU, P., WANG, F., WEI, H., WANG, X., XU, Z., LIU, F., SUN, X., & LI, J. (2016). Meloxicam suppresses hepatocellular carcinoma cell proliferation and migration by targeting COX-2/PGE2-regulated activation of the β-catenin signaling pathway. Oncology Reports, 35(6), 3614–3622. https://doi.org/10.3892/or.2016.4764

Loboda, A., Damulewicz, M., Pyza, E., Jozkowicz, A., & Dulak, J. (2016). Role of Nrf2/HO-1 system in development, oxidative stress response and diseases: an evolutionarily conserved mechanism. Cellular and Molecular Life Sciences, 73(17), 3221–3247. https://doi.org/10.1007/s00018-016-2223-0

M. M. H Shabuj, & Tufael. (2019). Advancing Personalized Treatment for Hepatocellular Carcinoma: Integrating Targeted Therapies, Precision Medicine, and Bioengineering for Improved Outcomes. Journal of Primeasia, 1.2(1), 1–14. https://doi.org/10.25163/primeasia.1110015

Md Abu Bakar Siddique, & Asim Debnath. (2018). Advancing Medical Science through Nanobiotechnology: Prospects, Applications, and Future Directions. Journal of Primeasia, 1(1), 1–10. https://doi.org/10.25163/primeasia.1110163

Mvondo, J. G. M., Matondo, A., Mawete, D. T., Bambi, S.-M. N., Mbala, B. M., & Lohohola, P. O. (2021). In Silico ADME/T Properties of Quinine Derivatives using SwissADME and pkCSM Webservers. International Journal of TROPICAL DISEASE & Health, 1–12. https://doi.org/10.9734/ijtdh/2021/v42i1130492

Pérez-Alvarez, I., Islas-Flores, H., Gómez-Oliván, L. M., & García, O. D. (2020). Teratogenesis and Embryotoxicity Induced by Non-steroidal Anti-Inflammatory Drugs in Aquatic Organisms (pp. 115–129). https://doi.org/10.1007/698_2020_545

Rojas, A., Chen, D., Ganesh, T., Varvel, N. H., & Dingledine, R. (2019). The COX-2/prostanoid signaling cascades in seizure disorders. Expert Opinion on Therapeutic Targets, 23(1), 1–13. https://doi.org/10.1080/14728222.2019.1554056

Sajadimajd, S., & Khazaei, M. (2018). Oxidative Stress and Cancer: The Role of Nrf2. Current Cancer Drug Targets, 18(6), 538–557. https://doi.org/10.2174/1568009617666171002144228

Tufael, & Auditi Kar. (2024). Diagnostic Efficacy of Tumor Markers AFP, CA19-9, and CEA in Hepatocellular Carcinoma Patients. Journal of Angiotherapy, 8(4). https://doi.org/10.25163/angiotherapy.849513

Tufael, & Md Mostafizur Rahman. (2024). Combined Biomarkers for Early Diagnosis of Hepatocellular Carcinoma. Journal of Angiotherapy, 8(5). https://doi.org/10.25163/angiotherapy.859665

Tufael. (2024). Hepatocellular Carcinoma in a 55-Year-Old with Chronic Hepatitis B: A Case Report on Diagnosis and Management. Asia Pacific Journal of Cancer Research, 1(1). https://doi.org/10.70818/apjcr.2024.v01i01.07

Tufael1, & Atiqur Rahman Sunny. (2023). Artificial Intelligence in Addressing Cost, Efficiency, and Access Challenges in Healthcare. Journal of Primeasia, 4(1), 1–5. https://doi.org/10.25163/primeasia.419798

Verras, M., & Sun, Z. (2006). Roles and regulation of Wnt signaling and β-catenin in prostate cancer. Cancer Letters, 237(1), 22–32. https://doi.org/10.1016/j.canlet.2005.06.004

Wang, J., Cho, N. L., Zauber, A. G., Hsu, M., Dawson, D., Srivastava, A., Mitchell-Richards, K. A., Markowitz, S. D., & Bertagnolli, M. M. (2018). Chemopreventive Efficacy of the Cyclooxygenase-2 (Cox-2) Inhibitor, Celecoxib, Is Predicted by Adenoma Expression of Cox-2 and 15-PGDH. Cancer Epidemiology, Biomarkers & Prevention, 27(7), 728–736. https://doi.org/10.1158/1055-9965.EPI-17-0573

Xu, D., Xu, M., Jeong, S., Qian, Y., Wu, H., Xia, Q., & Kong, X. (2019). The Role of Nrf2 in Liver Disease: Novel Molecular Mechanisms and Therapeutic Approaches. Frontiers in Pharmacology, 9. https://doi.org/10.3389/fphar.2018.01428

Xu, X., Huang, H., Tu, Y., Sun, J., Xiong, Y., Ma, C., Qin, S., Hu, W., & Zhou, J. (2021). Celecoxib Alleviates Radiation-Induced Brain Injury in Rats by Maintaining the Integrity of Blood-Brain Barrier. Dose-Response, 19(2). https://doi.org/10.1177/15593258211024393

Zhang, S., Gao, W., Tang, J., Zhang, H., Zhou, Y., Liu, J., Chen, K., Liu, F., Li, W., To, S. K. Y., Wong, A. S. T., Zhang, X., Zhou, H., & Zeng, J.-Z. (2020). The Roles of GSK-3β in Regulation of Retinoid Signaling and Sorafenib Treatment Response in Hepatocellular Carcinoma. Theranostics, 10(3), 1230–1244. https://doi.org/10.7150/thno.38711

Zhu, Y., & Hu, X. (2022). Molecular Recognition of FDA-Approved Small Molecule Protein Kinase Drugs in Protein Kinases. Molecules, 27(20), 7124. https://doi.org/10.3390/molecules27207124