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Computational exploration of curcumin–p-coumaric acid bioconjugates as potential inhibitors of β-catenin in breast cancer stem cells

ANANYA BAHUGUNA and SHIV KUMAR DUBEY*

Department of Biochemistry, College of Basic Sciences and Humanities, G. B. Pant University of Agriculture and Technology, Pantnagar-263 145 (U. S. Nagar, Uttarakhand)
**Corresponding author's email id: shivdub@gmail.com*

ABSTRACT: Breast cancer remains the most prevalent malignancy among women and a major contributor to global cancer mortality. The survival of breast cancer stem cells (BCSCs), regulated largely by the canonical Wnt/β-catenin signaling pathway, drives therapeutic resistance, metastasis, and tumor relapse.Contemporary chemotherapeutic strategies intended to target the transformed cells have not been proven to be effective due to recurrence, drug resistance, and poor prognosis, besides substantial toxicity to normal tissue too. Natural products including curcumin, a polyphenolic compound derived from *Curcuma longa* have been shown to possess pleiotropic therapeutic and chemopreventive properties along with their potential to inhibit Wnt-mediated stemness by suppressing the β-catenin, a key effector of the Wnt signaling pathway.The poor bioavailability and rapid metabolic degradation of curcumin have restricted its therapeutic use, thereby prompting the synthesis of curcumin-natural product conjugates. The present study employed an *in-silico* approach to analyse curcumin conjugates targeting β-catenin. A panel of ligand molecules, including curcumin, p-coumaric acid, its conjugate, and a reference β-catenin inhibitor (R9Q) were selected for the molecular docking process against the target protein, β-catenin. Molecular docking and interaction analysis revealed that the designed conjugates displayed improved binding affinity, and stability compared to native curcumin. These findings support the rational design of natural product-based conjugates as potential therapeutic leads targeting Wnt/β-catenin signaling in breast cancer stem cells.

Keywords: β-catenin, breast cancer stem cells, curcumin conjugates, molecular docking, Wnt signaling pathway

With a high global mortality and morbidity rate, cancer continues to be the oldest and major public health concerns of the 21st century. There are around 20 million new cancer cases and 9.7 million cancer deaths per year worldwide (Bray *et al*., 2024). Breast cancer particularly has become the most commonly diagnosed malignancy and leading cause of cancer deaths in women, with approximately 12% new cases and 25% prevalence among women (WHO, 2024). Although early diagnosis and targeted treatment have led to favourable outcomes in high-income countries, mortality rates are unacceptably high in low- and middle-income areas, with five-year survival often less than 40%, contrasting with greater than 80% in higher income settings (Francies *et al*., 2020; Kim *et al*., 2025). Therapy resistance, tumor heterogeneity, metastasis, and recurrence of the disease are major obstacles for curative success of cancer therapies that have grown more and are associated to the existence of cancer stem cells (CSCs).

CSCs are a unique subset of tumor cells that share characteristics with normal stem cells in terms of self-renewal, differentiation, and tumor-initiation potential. These cells are critically responsible for tumor recurrence and metastasis after subsequent conventional therapies because they are capable of surviving chemotherapy and radiation by going into a dormant phase, effectively repairing DNA breaks and up-regulating drug efflux transporters (Wang *et al*., 2025). Breast cancer stem cells (BCSCs) are recognized by their cell surface markers, such as $CD44^{-}/CD24^{-}$/low, ALDH1 positive and enhanced ability to generate self-renewing mammospheres (Liu and He, 2021). Their presence in the tumor microenvironment plays a role in both therapy resistance and progression of disease, as well as distant metastasis, thereby establishing their relevance for therapeutic intervention for long-term disease control (Gairola *et al*., 2025).

Among the hierarchies to stimulate the CSC self-renewal and pluripotency, emphasis is made on Wnt/β-catenin from the signaling pathways (Song *et al*., 2024). The β-catenin destruction complex (which

includes APC, Axin, CK1 and GSK-3β) is inhibited in the canonical Wnt pathway when Wnt agonist interact with their respective frizzled receptor and co-receptor LRP5/6. This causes β-catenin to stabilize and aggregate in the cytosol. It then translocates to the cell nucleus, in which it interacts through TCF/LEF factors which regulate transcription and activates target oncogenic genes, including MYC, Cyclin D1, and AXIN2 (Li *et al*., 2023; Nusse and Clevers, 2017). Numerous cancer types, including breast, colorectal and liver carcinomas have shown to impair this pathway, either by mutation or uncontrolled stimulation.In breast carcinoma, continuous stimulation of Wnt/β-catenin signaling induces the epithelial-mesenchymal transition (EMT), enhances CSC properties, and is linked to a poor medical outcome (Xu *et al*., 2020).Therefore, the therapeutic regulation of Wnt signaling stands out as a good alternative that could be used to eliminate CSCs and inhibit tumor relapse.

As producers of multitargeted anticancer bioactive chemicals, natural products have garnered significant attention lately.Their inherent structural heterogeneity, biocompatibility, and capacity to regulate several signaling cascades make them perfect CSC-targeted therapy candidates (Hashem *et al*., 2022). A number of phytochemicals like resveratrol, epigallocatechin gallate, genistein and curcumin have been reported to mediate CSC survival and differentiation by regulating the Wnt, Notch, Hedgehog and PI3K/Akt pathway (Gairola *et al*., 2021). In addition, natural products tend to possess reduced systemic toxicity and better tolerability, and are thus appropriate as a long-term chemoprevention or combination therapy.

Of these, curcumin, a polyphenolic diketone derived from *Curcuma longa* (turmeric), has proven to have exceptional potential because of its anti-inflammatory, antioxidant, and anticancer properties (Wang *et al*., 2023). Curcumin exhibits a broad spectrum of cellular activities and has proven to influence growth factor receptors, kinases, transcription factors (NF-kB, STAT3), and enzymes (COX-2, LOX, MMPs) that regulate cancer. Curcumin is known and has proven in numerous studies to be able to disrupt the Wnt/β-catenin signaling pathway, thus suppressing CSC properties in various malignancies. Curcumin suppresses the expression of β-catenin, inhibits its nuclear translocation, and suppresses the transcription of oncogenes by TCF/LEF (Hegde *et al*., 2023; Liang *et al*., 2023). It also increases the degradation of β-catenin through stimulating GSK-3β and down regulating the expression of Wnt ligands efficiently interfering with the process of CSC maintenance and self-renewal (Yu *et al*., 2020). In breast cancer, curcumin is shown to decrease mammosphere formation, reduce the population of ALDH+ and CD44+/CD24- cells, and sensitize resistant cells to chemotherapy (Charpentier *et al*., 2014; Zhu *et al*., 2024).

Current research has attempted to formulate curcumin conjugates and derivatives that are extremely stable, bioavailable, and target-specific with the intention to overcome these pharmacokinetic obstacles. By facilitating better interactions with the components of the Wnt pathway, these molecular alterations can enhance curcumin's pharmacodynamics and perhaps boost its detrimental influence on CSC-related signaling (Harikrishnan *et al*., 2021).Curcumin bioconjugates made with various ligands have been researched and shown to have superior antibacterial and antiproliferative properties compared to the native curcumin (Abd El Hack *et al.,* 2021; Dubey *et al*., 2008). Thus, the objectives of the current study include: *in-silico* assessment of curcumin-p-coumaric acid conjugates to address the limitations on the pharmacokinetic properties of curcumin as mentioned above. This conjugation hypothesis is intended to enhance the molecular stability, lipophilicity, and cellular permeability of curcumin, thereby increasing its anticancer effect and its ability to regulate Wnt/β-catenin signaling pathway in breast cancer stem cells.

In-silico molecular docking and pharmacokinetic analyses were employed to identify conjugates with optimal binding affinity towards β-catenin and favourable drug-likeness properties. It is

hypothesized that the resulting conjugates will improve the anticancer effects of the Wnt/β-catenin signaling pathway, which is a key mediator of breast cancer stem cell development and viability. Moreover, p-coumaric acid is a naturally occurring byproduct of hydroxycinnamic acid that is reported to demonstrate considerable anticancer, antioxidant, and anti-inflammatory effects in different tumor models. In recent years, it has been revealed that p-coumaric acid can suppress the Wnt/β-catenin signaling pathway, which causes decreased β-catenin nuclear translocation and the inhibition of oncogenic transcriptional targets (Kaleem *et al*., 2024; Tehami *et al*., 2023). Thus, this work is novel in proposing and validating, through *in-silico* approaches, curcumin-p-coumaric acid bioconjugates as synergistic molecules that enhance curcumin's stability and bioavailability while specifically attenuating β-catenin dependent stemness signaling in breast cancer.

MATERIALS AND METHODS

Ligand Design and Preparation

The parent molecules used to design these conjugates were curcumin and p-coumaric acid, which have been documented to have anticancer and Wnt pathway modulator effects.To improve the physicochemical stability and bioavailability of curcumin using the strategy of molecular hybridization, a series of curcumin-p-coumaric acid conjugates were designed. The ligand structures of curcumin and p-coumaric acid were downloaded from the PubChem repository in SDF file format, and Open Babel 2.4.1 was used to import them into PDB format.The reference β-catenin inhibitor R9Q was downloaded in CIF format at RCSB Protein Data Bank (https://www.rcsb.org) and conjugates of the monoester and diester were sketched in SKC format with ChemDraw Ultra 12.0 (PerkinElmer, USA) and optimized using MM2 molecular dynamics. Open Babel was then used to translate the reference inhibitor and the conjugates to PDB format (O'Boyle *et al*., 2011) to obtain the best conformations before *in-silico* molecular docking experiments as depicted in Fig 1.

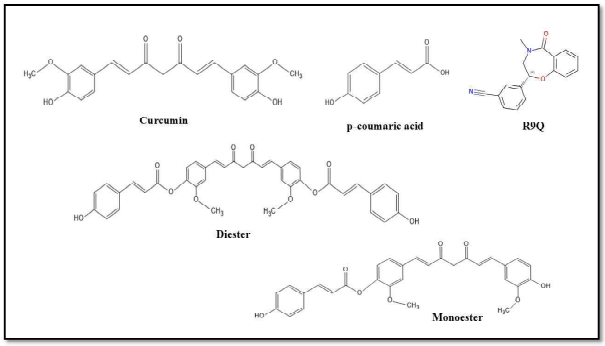

Fig1: 2D structure of curcumin, p-coumaric acid, their conjugates (diester & monoester) and known binder

Protein Structure Retrieval and Preparation

Since the β-catenin protein is crucial to the canonical Wnt signaling and stemness regulation in breast cancer, it was selected as the molecular target.The RCSB Protein Data Bank (https://www.rcsb.org) provided the three-dimensional crystal form of human β-catenin (PDB ID: 7AFW) with a resolution that allows molecular docking analyses.The specific PDB structure was chosen based on several quality

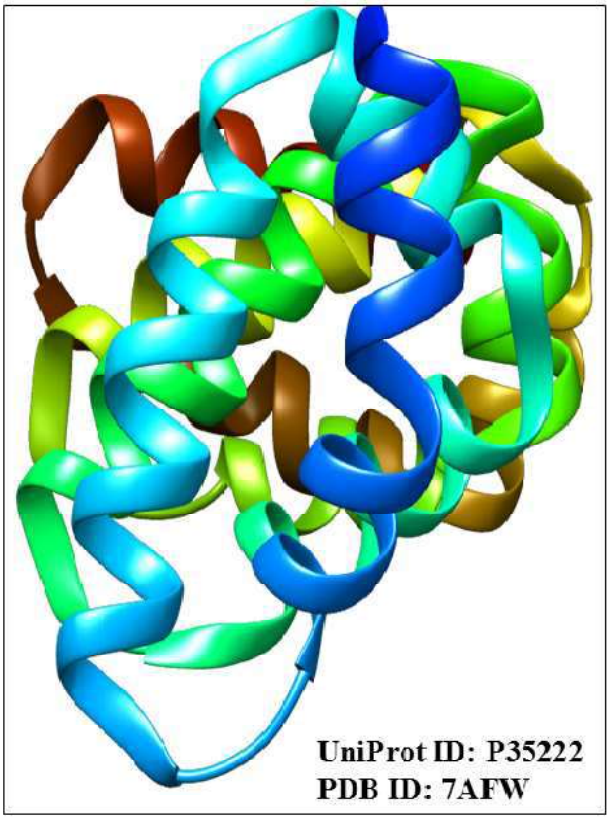

Fig 2:The 3D structure of β-Catenin protein

assessment aspects such as a high crystallographic resolution, moderate R-factor values that suggest a great conformity between experimental and modelled data, and coverage of the entire protein sequence, thus providing a precise and reliable representation of functional and structural domains of the protein. UCSF chimera 1.17.3 was utilized to optimize the protein structure prior to docking (Butt *et al*., 2020), during which all the water molecules, heteroatoms, and the co-crystallized ligands were removed to avoid steric hindrance and provide a true binding site accessibility. To improve the docking environment, polar hydrogen atoms were added to the protein structure. The binding residues of β-catenin as reported previously through the UniProt Knowledgebase (UniProt ID: P35222) were used to identify the binding site area.This was followed by the saving of the prepared protein structure in the PDB format, which could be used later in molecular docking as depicted in Fig 2.

Molecular Docking Protocol

Using AutoDock Vina, which is integrated into the PyRx software (Trott and Olson, 2010), molecular docking investigations were conducted to examine the binding affinity and orientation of the ligands in the human β-catenin binding pocket (PDB ID: 7AFW). Firstly, the created PDB files of the target protein and associated compounds were imported into PyRx. The macromolecule was then made the target protein and the grid box was configured to approximate dimensions, including the active site region that interacts with β-catenin and TCF. The ligands were subsequently introduced to the docking platform one at a time. To make the ligands compatible with AutoDock Vina, they underwent energy minimisation and were transformed to the '.pdbqt' format. The least energy orientations were identified using binding affinity scores (kcal/mol), acceptable RMSD values (≤2 Å), and consistency of ligand orientation between docking runs. The docking conditions were configured with default exhaustiveness value of 8. The dimensions for grid center, in angstrom, were X: 35.4682, Y: 38.0439, Z: 48.4857 and the box coordinates values were X: 70.1643, Y: 30.7945, Z: 22.3801. Visualization and analysis of hydrogen bonds, hydrophobic interactions, and π–π stacking were conducted using Discovery Studio Visualizer 2023. R9Q is a well-known β-catenin binder, which was added as a positive control that allowed a comparative assessment of docking performance.

RESULTS AND DISCUSSION

Recognition of Target Protein

The target protein in this *in-silico*investigation was the human β-catenin protein, which is involved in cellular proliferation, differentiation, and stemness and is a crucial modulator of the classical Wntsignaling pathway. Aberrant activation of β-catenin has been strongly associated with tumor initiation, progression, therapeutic resistance, and the preservation of breast cancer stem cell phenotypes, thereby making it a highly relevant therapeutic target (Mishra *et al*., 2019). Because of its high quality structural resolution (1.81 A), which ensures high precision in the depiction of the atomic coordinates, the corresponding crystalline model with PDB ID: 7AFW was chosen to examine docking among the known crystalline models of β-catenin in the RCSB Protein Data Bank (PDB).

The protein of interest has a molecular mass of 18.45 kDa and contains 1,314 atoms ordered in 167 amino acid residues among which 161 residues are properly resolved and can be employed for the further analyses.The crystal structure is a single unique polypeptide chain, giving it a stable and well-defined interaction interface with the ligand. This structural integrity and resolution enable accurate determination of the β-catenin-TCF interaction domain, and enable good docking and interaction profiling on curcumin and its designed curcumin-p-coumaric acid conjugates.The preservation of significant functional motifs and secondary structural components within the armadillo repeat domain of 7AFW justifies its use as a reliable model for investigating potential inhibitors of β-catenin-mediated oncogenic signaling cascade in breast cancer stem cells.

Molecular Docking and Interaction Analysis

The outcome of molecular docking showed that

Table 1: Comparative docking simulation result of Curcumin, its Conjugates (Diester and Monoester), p-coumaric acid and Known binder (R9Q) with Beta Catenin

Name of the ligand	Residues	Binding Free Energy (kcal/mol)
Curcumin	Gln203, Asn204, Thr205, Asn206, Lys242, Met243, Gly245, Pro247, Lys281	-5.6
Diester	Gln203, Asn204, Thr205, Asn206, Lys242, Met243, Pro247	-7.3
Monoester	Lys292, Tyr254, His219, Thr257, Phe253, Ser250, Asn290, Phe293, Asp249, Lys288, Leu252	-7.0
p-coumaric acid	Asn290, Phe253, Asp249, Phe293, Leu252, Lys288	-5.1
R9Q (Known Binder)	Thr289, Asp249, Phe293, Lys288, Asn290, Phe253, Ser250	-7.6

curcumin, p-coumaric acid, their conjugates, and the reference β-catenin inhibitor R9Q had different binding affinities. Docking scores were determined ranging from -5.1 to -7.6 kcal/mol signifying high ligand-receptor affinity in the β-catenin active site. The binding energies of curcumin-p-coumaric acid conjugate (diester) and curcumin-p-coumaric acid conjugate (monoester) were -7.3 kcal/mol and -7.0 kcal/mol respectively, surpassing the binding energies of the native curcumin (-5.6 kcal/mol) and p-coumaric acid (-5.1 kcal/mol), and closely comparable to the binding energy of known binder i.e., R9Q (-7.6 kcal/mol) as mentioned in Table 1.

To stabilize the β-catenin-TCF complex, extensive interaction mapping revealed that the conjugate established numerous hydrogen bonds using key residues-Lys312, Asp299 and Asn287 within the β-catenin binding interface (Song *et al*., 2024). Further, hydrophobic interaction with residues Phe293, Tyr333 and Leu383 also promoted ligand anchoring (Table 1, Fig 3). Interestingly, curcumin had fewer stabilizing hydrogen bonds and weaker π–π stacking than its conjugate, indicating that structural

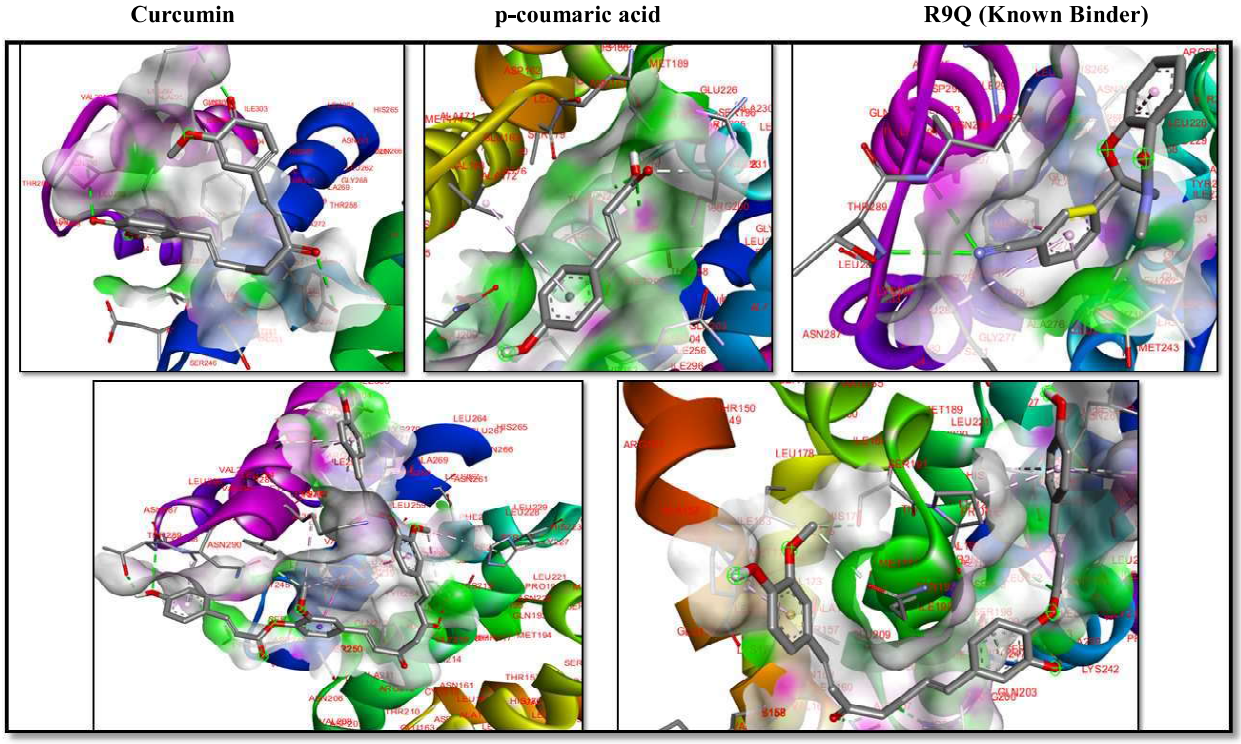

Fig. 3: 3D representation of docked conformation of curcumin, p-coumaric acid, their conjugates (diester & monoester) and known binder using Discovery Studio

extension with p-coumaric acid enhanced molecular complementation and surface coverage of the binding pocket (Fig 3). The structural extension achieved through conjugation with p-coumaric acid appears to facilitate improved interaction geometry and binding stability.

The Wnt/β-catenin pathway has a key role in sustaining breast cancer stem cell (BCSC) self-renewal, survival, and treatment resistance. The curcumin-p-coumaric acid conjugate's greater binding affinity for β-catenin suggests that it may prevent the formation of the β-catenin-TCF/LEF complex, hence preventingthe transcriptional activation of Wnt specific proteins such as Cyclin D1, MYC and AXIN2. This mechanism is consistent with previous results indicating curcumin and its analogues suppress β-catenin nuclear localization and promote proteasomal degradation (Shen *et al*., 2025). In addition, p-coumaric acid has been reported to modify β-catenin phosphorylation and reduce Wnt ligand expression, indicating synergistic interference with signaling pathway when conjugated with curcumin (Nazam *et al*., 2023). Therefore, curcumin-p-coumaric acid conjugate can have dual mechanisms of action- destabilization of β-catenin and inhibition of upstream Wnt signaling genes, therefore, targeting the population of BCSCs that leads to relapse and metastasis.

CONCLUSION

The current *in-silico* study offers a complete structural and molecular understanding of the possibilities of curcumin- p-coumaric acid conjugates as novel regulators of the Wnt/z β-catenin signaling cascade in breast cancer stem cells. The molecular docking results revealed that the conjugates designed have an increased binding affinity and a higher stability than native curcumin. These results indicate that the strategic conjugation of p-coumaric acid enhances the bioavailability and metabolic stability of curcumin in addition to increasing the ability of curcumin to deactivate β-catenin-mediated oncogenic signaling. Due to the centralization of Wnt/β-catenin dysregulation in sustaining stemness and treatment resistance in breast cancer, these conjugates represent one of the most promising target-specific chemopreventive or adjuvant therapeutic options. Further, this computational research report supports the significance of structure-guided rational design in improving the pharmacological features of natural bioactives. These findings provide a basis to further *in vitro* and *in vivo* validation of the biological efficacy, mechanism of action and pharmacodynamic behaviour of these conjugates. Together, the research contributes to the knowledge about curcumin-driven drug design and offers a future perspective of synthesizing natural product-based therapeutics to combat the curcumin-driven signaling networks of cancer stem cells.

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