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Research Article

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Molecular Docking Studies to Evaluate Small Molecule Inhibitors of Wnt/Betacatenin Signaling Pathway

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Abstract: Canonical Wnt pathway or β catenin dependent pathway is one of the highly conserved signalling pathway which can control gene expression and regulate cell proliferation, cell adhesion, cell migration, cell polarity and organogenesis. Abnormal regulation of β catenin in the canonical wnt signalling pathway leads to transcription of several genes involved in oncogenic programs. Aberrant signalling of the canonical wnt pathway was observed in several types of cancers including hepatocarcinoma, colorectal cancer and lung cancer. Many small molecules were observed to have the potential to block the aberrant wnt signalling pathway by allosteric binding and inhibiting β catenin molecule. The current study involves screening for ligands which can have strong allosteric binds to β catenin and inhibit wnt signalling pathway. Molecular docking studies were used to evaluate the binding capacity of the selected ligands. Curcumin, Cardamonin, FH535 and ICRT-3 were used as ligands for the molecular docking study with β catenin binding Transcription factor -4 receptor. All chosen ligands have exhibited significant binding energies with the receptor. The highest -9.518272 kcal/mol with Cardamonin followed by -9.28359 kcal/mol with FH535, -8.422604 kcal/mol with curcumin and the least -8.407231 kcal/mol with ICRT-3. All the ligands showed at least 1 hydrogen bond with the target receptor whereas Cardamonin showed 3 hydrogen bonds. Curcumin is a close second forming 2 hydrogen bonds while FH535 and ICRT-3 form only 1 hydrogen bond. The 2D interactions of the ligand and the molecule are visualised by using chimera. We observed Cardamonin to have a very strong binding affinity with the target receptor. Cardamonin can be a suitable drug candidate and might have the potential to inhibit the β catenin dependent wnt signalling pathway.

Keywords: Wnt, β catenin, Signalling pathway, Cancer, Small molecule inhibitors

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1. INTRODUCTION

The wnt-signalling pathways are a set of signal transduction cascade which begins with transfer of signals into the cell through its cell surface receptors.[1-3] There are three major wnt- signalling pathways and all three pathways get activated by the binding of a wnt- protein ligand to a frizzled G protein coupled receptor, which passes the biological signal to the disordered protein inside the cell.[4-6] The wnt/beta-catenin pathway plays a crucial role in cancer development and progression by stimulating the cytoplasmic accumulation and activating genes involved in cancer cell proliferation, anti-apoptosis, cell cycle progression, and cell invasion.[7-9] This signalling pathways regulates the expression of a variety of tumor- related proteins, including c-myc and cyclin D1, Small molecules which can bind to β-catenin and prevent the downstream signalling cascade of Wnt/β-catenin pathway can act as novel class of anticancer drugs.[10-13] The canonical wnt signalling pathways is the best studied wnt pathway and is greatly conserved through the evolution. In this pathway, wnt signalling inhibits the degradation of beta- catenin which can regulate transcription of several genes. The wnt beta-catenin signalling pathways typically show abnormal activation in various types of cancers especially in colorectal cancer.[14-16] Wnt signaling was identified initially for its function in carcinogenesis, then for its role in embryonic development. Wnt signalling has been involved in the development of several types of cancers.[17,18] Abnormal changes in CTNNB1 (i.e., gene encoding β-catenin) gene expression can be measured in breast, colorectal, melanoma, prostate, lung, and several other cancers.[19,20] The recently identified β-catenin/Tcf inhibitors also share structural resemblance to the known PPARγ antagonists. All the compounds contain the nitro group, differing mostly in the central amide or sulfonamide groups as well as their initiation. FH535 is one of the most active compounds which can antagonize both PPARγ and wnt signalling.[21,22] FH535 was chosen as an ideal candidate for allosteric binding of β-catenin. Curcumin is the major yellow pigment and spice in turmeric and curry and is a powerful anti-cancer agent. Studies indicate that curcumin has anti-tumor effects on several cancers, including Colorectal cancer. The anti-tumor activity of curcumin was observed to be due to the blockade of the Wnt/β-catenin pathway and inhibiting the proliferation of colon cancer cells. This process was regulated by repressing the expression of microRNA (miR)-130a, and overexpressing miR-130a could completely abolish the curcumin-induced anti-tumor activity in colon cancer.[23,24] Cardamonin is a spice derived nutraceutical. Therapeutic benefits of cardamonin were observed in Azoxymethane (AOM) induced mouse model of colorectal cancer. Cardamonin treatment inhibited the tumor incidence, tumor multiplicity, Ki-67 and β-catenin positive cells.[25,26] ICRT-3 is a small cell permeable oxazole compound. ICRT-3 was observed significantly decreasing the expression of genes involved in cell migration and found having inhibitory effect on Wnt signalling pathway.[27,20] These four small molecule ligands i.e., ICRT-3, Cardamonin, curcumin and FH535 were chosen of the study to evaluate their allosteric binding capacity to β-catenin. In this study we have evaluated allosteric binding capacity of four potential small molecule inhibitors (i.e., ICRT-3, Cardamonin, curcumin and FH535) of Wnt/Betacatenin signalling pathway using molecular docking studies.

2. MATERIALS AND METHODS

2.1 Selection and retrieval of the target protein

Beta-catenin is the target molecule for this study. It plays a crucial role in the replication process of cancer cells. The three-dimensional co-crystallized structure of Beta-catenin with Transcription factor-4 (TCF-4) was retrieved from RCSB Protein Data Bank (PDB entry: 1JPW) presenting a resolution of 2.50 Å with total of 1620 residues (chains A, B and C) and approximately 150.51kDa molecular mass. The molecule is uploaded into Swiss Dock in PDB format where it is prepared for the docking by removing the water molecules, metal ions and ligands, followed by addition of polar, non-polar hydrogen atoms and adding kollman charges. Finally, rotatable bonds are assigned to the molecule making it suitable for further analysis.

2.2 Retrieval and Preparation of ligand

The 3D structures of the ligands FH535(ZINC4662683), Curcumin (ZINC899824), ICRT-3(ZINC5057585), Cardamonin (ZINC4716487) are selected and retrieved from PubChem and ZINC database. The structures were prepared by using SwissDock by assigning flexible torsions and were allowed to rotate freely.

2.3 Protein ligand molecular docking

The molecular docking was done by online bioinformatic tool Swiss Dock. The target and ligands were prepared for docking as mentioned in the above two steps. Binding molecules are created in the region of the target molecules, and their CHARMM energies are estimated on the grid. The binding modes with the most favourable energies are evaluated with FACTS and assembled. The most favourable clusters are grouped, and the results are downloaded.

3. STATISTICAL ANALYSIS

Docking studies with all the four ligands were performed five times. The binding energies (ΔG) shown in Table 1 are the average of five experiments. We found all the values obtained from docking studies were statistically significant ($p<5\%$).

4. RESULTS AND DISCUSSIONS

Molecular docking of the target receptor was done with synthetic as well as natural ligand. The 3D structure of Beta-catenin binding with Transcription factor-4 (1JPW) (Figure 1) was obtained from PDB. The ligands used for the analysis are FH535, ICRT-3, Cardamonin and Curcumin (Figure 2). The structures were downloaded from the ZINC database. These four ligands were docked on to the β catenin (1JPW) receptor.

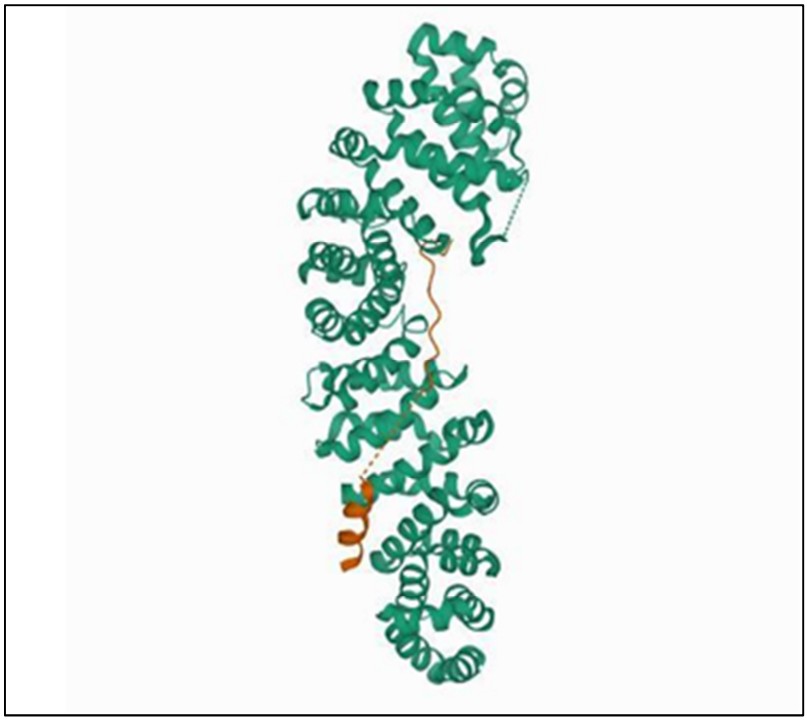

Fig1: Crystal Structure of a Human Tcf-4 / β catenin Complex

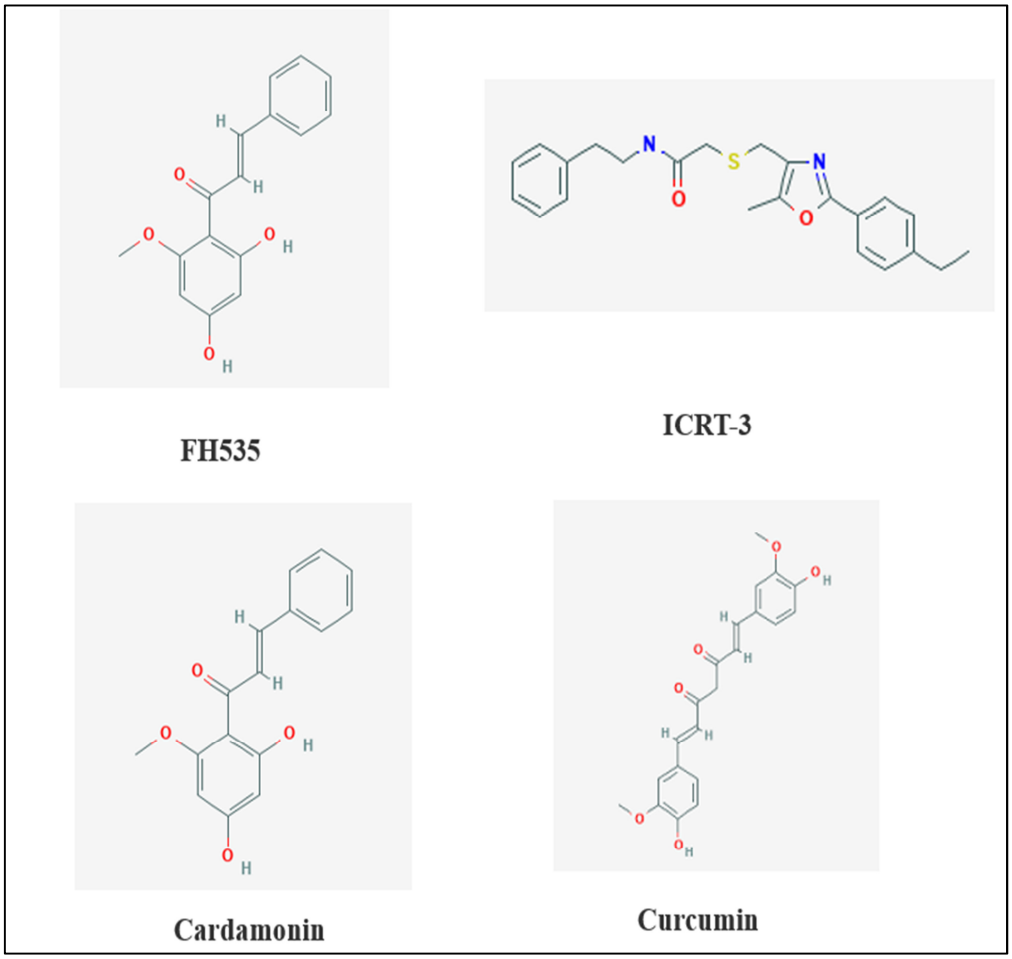

Fig 2: Structures of small molecule inhibitors used as ligands

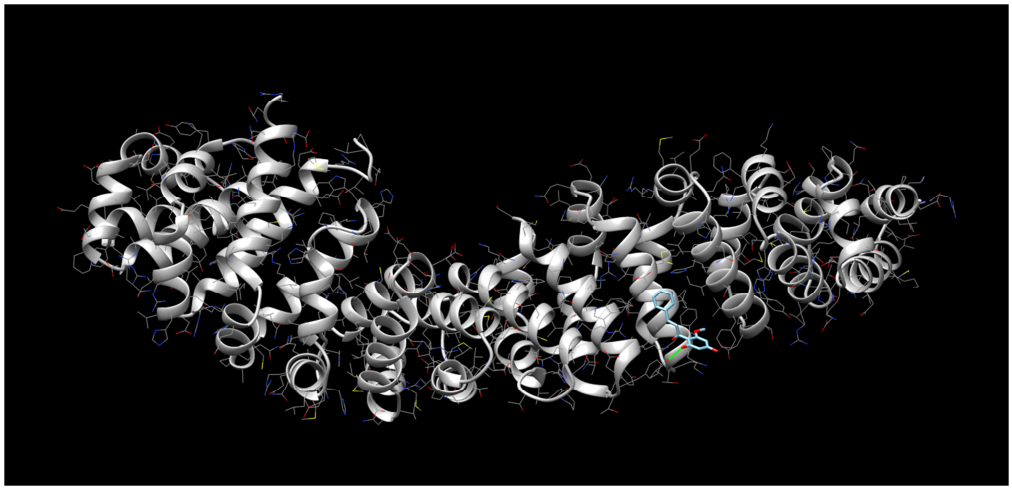

Fig 3: Interaction of ligand molecule cardamonin with β catenin

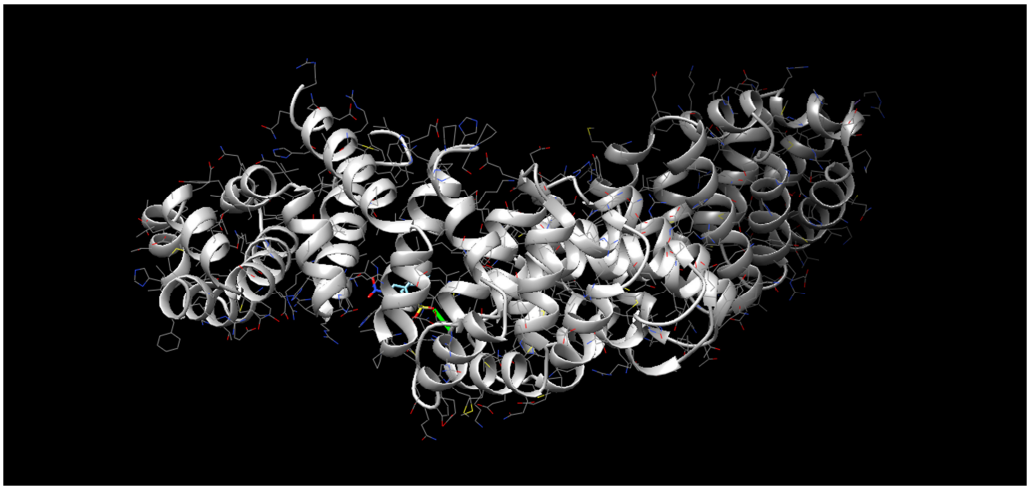

Fig 4: Interaction of ligand molecule FH535 with β catenin

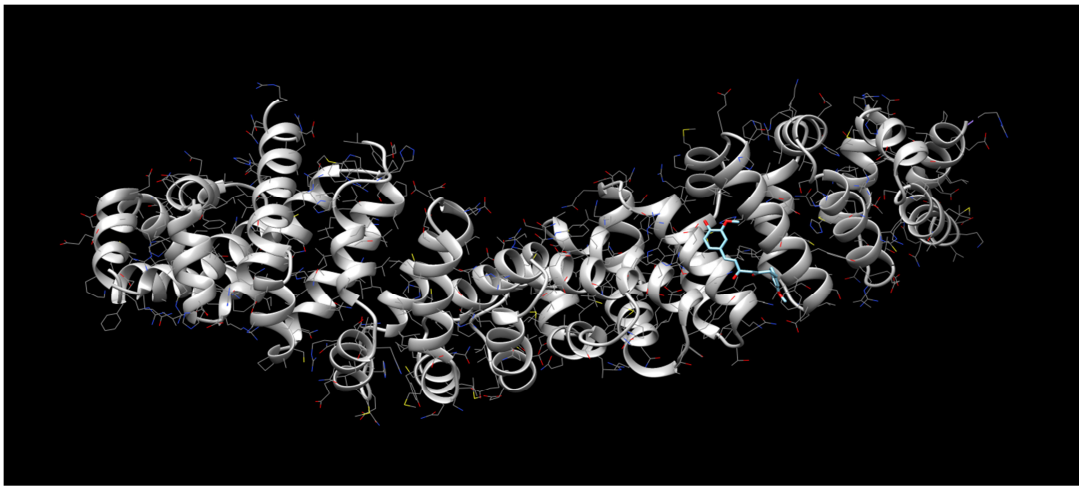

Fig 5: Interaction of ligand molecule curcumin with β catenin

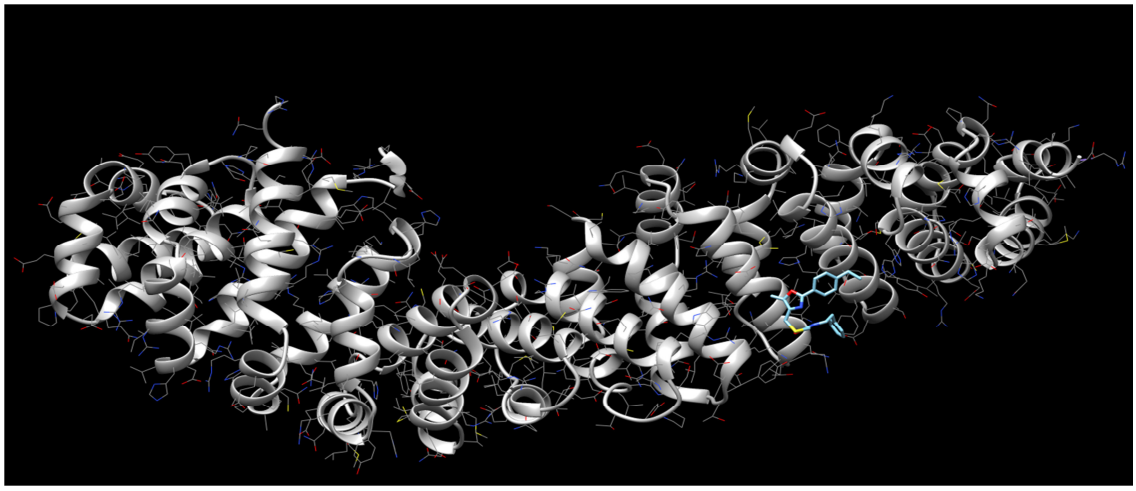

Fig 6: Interaction of ligand molecule ICRT-3 with β catenin

Since Swiss Dock cannot analyse large molecules, the ligands were docked on to the individual chains (Chain A, B, C) of the β catenin and the results were cumulated for the final analysis. The target receptor i.e., β catenin exhibited significant binding energies with the ligands. The highest -9.518272kcal/mol with Cardamonin (Figure 3) followed by FH535 with -9.28359 kcal/mol (Figure 4), binding energy of -8.422604 kcal/mol was observed with curcumin (Figure 5) and the least binding energy of -8.407231 kcal/mol with ICRT-3 (Table 1) (Figure 6). All the ligands showed a minimum of one hydrogen bond with the target receptor. Cardamonin showed 3 hydrogen bonds with the target Curcumin being a close second forming 2 hydrogen bonds whereas FH535 and ICRT-3 formed only one hydrogen bond. The 2D interactions of the ligand and the molecule were visualised using chimera. We observed Cardamonin having very strong interaction with β catenin possibly inhibiting the pathway. In a recent study cardamonin was reported inhibiting the gastric cancer cells through Wnt/ β catenin signalling pathway[28] also it showed strong anti-tumour activity *invitro* on breast cancer cell lines.[29] Cardamonin was also reported to suppress melanogenesis and proliferation of colon cancer by inhibiting Wnt/Betacatenin signalling pathway.[30,31] Curcumin which came as a close second in our binding studies recently reported showing ovarian cancer cells and non-small-cell lung cancer inhibition also reported suppressing colan cancer and hepatocarcinoma proliferation *invitro* by modulating Wnt/ β catenin signalling pathway.[32-35]

Table 1: Binding energies and hydrogen bonding of ligands with β catenin

Ligand	Delta G	Hydrogen bonds	Full fitness	Delta G VDW
FH535	-9.28359	1	-2514.6306	-91.0673
Curcumin	-8.422604	2	-2551.7612	-55.7558
ICRT-3	-8.407231	1	-2530.5212	-52.4458
Cardamonin	-9.518272	3	-2545.0784	-105.883

5. CONCLUSION

Wnt/β- Catenin signalling is critically involved in cell proliferation and migration during embryonic development. Aberrant regulation of Wnt/β- Catenin signalling leads to several types of cancers. Small molecule inhibitors can be novel drug candidates for allosteric binding of β- Catenin and blocking the Wnt/β- Catenin signalling pathway. In this study we used fourpotential natural and synthetic small molecule inhibitors as ligands to evaluate the allosteric binding capacity to β-catenin and inhibition of Wnt/β- Catenin signalling pathway. We observed Cardamonin to have very strong binding affinity with the β- Catenin receptor. Cardamonin can be a suitable drug candidate and might have the potential to inhibit the β catenin dependent wnt signalling pathway.

6. ACKNOWLEDGEMENT

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7. AUTHOR CONTRIBUTION STATEMENT

Chandrasekhar Chanda conceived the idea and supervised the finding of this work. Dantu Sai Shyama Lakshmi Sankari and Sai Sailaja Maka analyzed the data and necessary inputs were given towards the designing of the manuscript. Swetha dalal involved in manuscript writing and statistical analysis. Chandrasekhar Chanda involved in manuscript corrections. All authors discussed the methodology , results and contributed to the final manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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