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In-Silico docking studies of natural biotherapeutic agents on human notch receptor

Sathish Babu P., Anand Babu K.*, Sujatha K. and Chitra K.

Faculty of pharmacy, Sri Ramachandra University, Porur, Chennai

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ABSTRACT

The Notch signaling pathway is an evolutionarily conserved cell signaling system, which regulates cell proliferation, cell fate, differentiation, and cell death in all metazoans. The notch receptor is a single-pass trans-membrane receptor protein which contains four Notch homologues, NOTCH1, NOTCH2, NOTCH3, and NOTCH4 identified in the human genome and aberrant Notch function has been associated with a number of human diseases including Cancer and it also plays a key role in modulating cell fate decisions throughout the development of invertebrate and vertebrate species. The focus of this article primarily depends on the literature evidence that many phytochemicals i.e., chief chemical moieties of various plants show a great significance in the regulation of this notch signaling pathway. Some of these phytochemicals include Resveratrol, Curcumin, Genistein, Sulforaphane, Isooquercitinin, Koenimbin, Withaferin. So the chemical structures of these phytochemicals were taken and in-silico molecular docking was done with the notch receptor to show the Energy binding values. With these values it can be concluded that these phytochemicals can be used as biotherapeutics in regulating the notch thus making alterations in the Notch signaling system and achieving an effective contrivance in treating diseases right from embryogenetic disorders to cancer stem cells. Thus this regulation of the notch signaling pathway will serve to be a breakthrough in the pharmaceutical world using phytochemicals as biotherapeutics.

Keywords: Molecular docking, Natural Biotherapeutic agents, Human Notch Receptor.

INTRODUCTION

In structural molecular biology and computer assisted drug design Molecular Docking is used as a key tool. The objective of ligand-protein docking is to prognosticate the predominant binding site of ligand with a protein of known three dimensional structure. NOTCH SIGNALLING PATHWAY is an evolutionarily conserved cell signaling system, which regulates cell proliferation, cell fate, differentiation, and cell death in all metazoans.[1] The Notch receptor contains four Notch homologues, NOTCH1, NOTCH2, NOTCH3, and NOTCH4 identified in the human genome which is a single pass trans membrane protein. Many aberrant Notch function has been associated with a number of human diseases including Cancer and it also plays a key role in modulating cell fate decisions throughout the development of invertebrate and vertebrate species. [2-4]

Computer-aided drug design (CADD) is a screamingly evolving field that leverages new data and methods to provide approaches for tackling the needs of drug discovery. The docking of the ligand molecule with the desired protein is one such method. The site of drug action, the receptor, is ultimately responsible for the pharmaceutical effect. Molecular Docking is the process by which two molecules fit together in 3D space. [5]

The aim of the present work is to associate this concept with protein based molecular docking using natural biotherapeutic agents as ligands and the notch receptor as the protein and understand their importance.[6,7] The objective is to obtain 3- dimensional figures of the receptors and the phytochemicals and Dock them using computer softwares. With these inferences it can be concluded that these compunds can be effectively used to target the Notch signalling pathway. This will be the first of its kind to dock the Human notch extensively with Natural compounds. The plan of the work was to obtain the 3D structures of the protein and of the natural molecules and to Dock them using appropriate softwares and to determine their efficacies respectively.

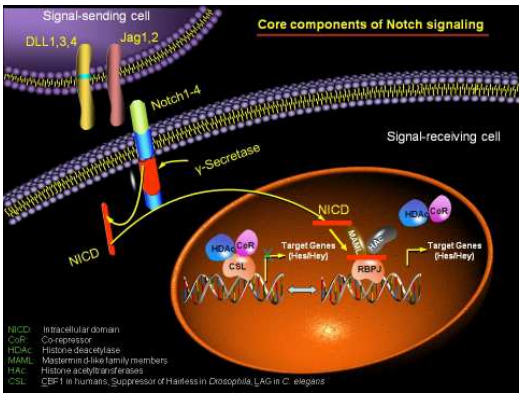


Fig.No.:1: Mechanism Of Notch Receptor

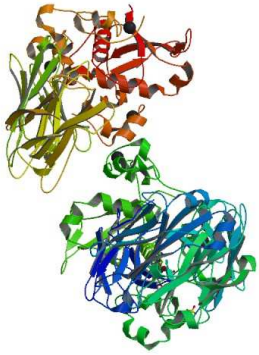
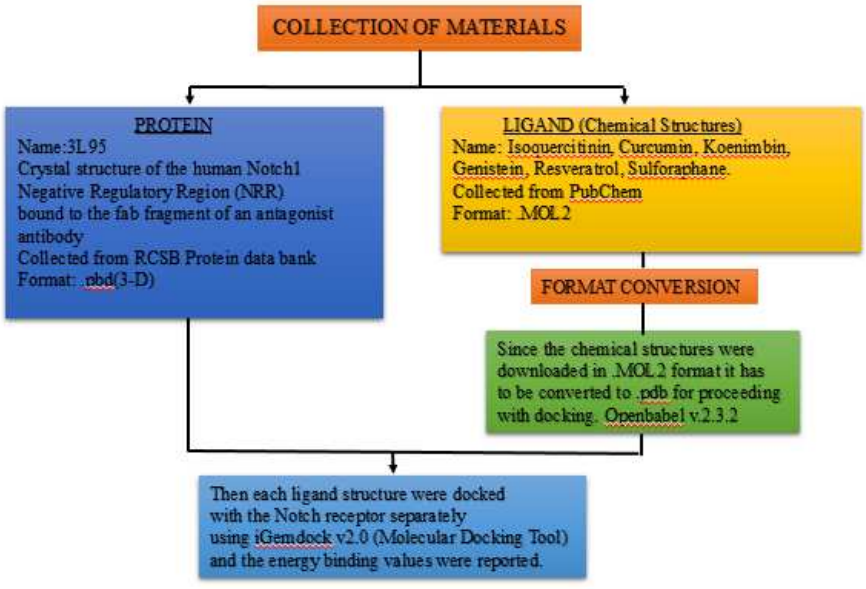


Fig.No.:2: Human Notch-1 Protein

MATERIALS AND METHODS

Softwares and Data Sources: The software used were all obtained from the internet free of cost. The Protein Structure was collected from the RCSB Protein data bank. The ligand Structures were downloaded from PUBCHEM. The docking simulation was performed using HEX Docking Tool. A Brief flow on the data ccollection and Method has been defined in the flow chart-1. [8-10]



Flow Chart-1: Materials and method

The default Hex and default evolutionary parameters were used to perform the Docking experiments.: correlation type – shape only, FFT mode – 3D fast lite, grid dimension – 0.6, receptor range – 180, legend range – 180, twist range – 360, distance range – 40. [11]

RESULTS AND DISCUSSION

Generally, Before each docking run, HEX allows the given receptor and the ligand residue to rotate onto the z-axis. Thus an effective docking of the ligand on almost all sites for the receptor to possibly attach are well predicted and docked in HEX. The docking results are shown in Table 1 and 2 respectively. The docked poses of all the ligands are shown in the figures 3 to 8.. All the compounds have showed NEGATIVE VALUES i.e., All the compounds have greater affinity towards the receptor. Thus these compounds can be effectively used in regulating the Notch signalling pathway. Among all the compounds, Isoquercitinin has found to show a very high energy binding value showing that it can be effectively used

Table-2 briefly explains about the complete summary of the docking process. Similarly as mentioned above, isoquercitinin was found to have a very high energy binding value and it also has most number of vanderwal's interactions, Hydrogen bond interactions and increased average connecting pairs.

Table no.:1: Energy binding values of the docked ligands with the Notch receptor

Name of the compound	Code of the compound	Chief Source	Energy Binding values
Curcumin	C1	Turmeric,Cauliflower,Cabbage,Brocoli	-97.4434
Genistein	C2	Psoralea, Soybeans, Lupin	-91.6219
Isoquercitinin	C3	Apple, Onion	-126.87
Koenimbin	C4	Murraya Koenigii (Karuvveppilai)	-94.45
Resveratrol	C5	Peanuts, Grape, Chocolate, Red and white wine	-85.474
Sulforaphane	C6	Cabbage, Brussels sprouts, Broccoli, Sprouts	-65.975

Table No.2: Summary analysis of the human notch receptor and natural biotherapeeutics

Name of the compound	Total Energy	Vanderwal's Interactions (VDW)	Hydrogen Bonds (HBond)	Average Connecting Pairs (AverConPair)
CURCUMIN	-97.4434	-81.1914	-16.2519	27
GENISTEIN	-91.6219	-67.9129	-23.709	28.1
ISOQUERCITININ	-126.87	-73.8189	-53.0516	23.2424
KOENIMBIN	-94.45	-81.7786	-12.6714	35.7727
RESVERATROL	-85.474	-69.8567	-15.6174	29.0588

DOCKED POSES

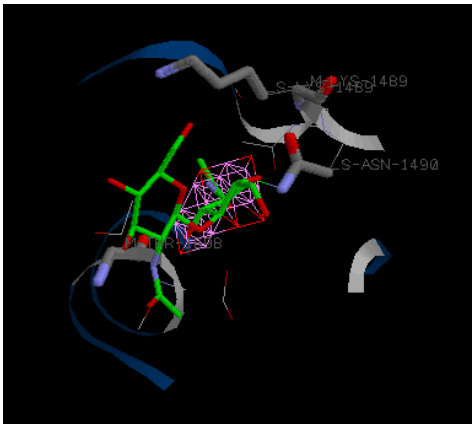


Fig. No.:3: C1

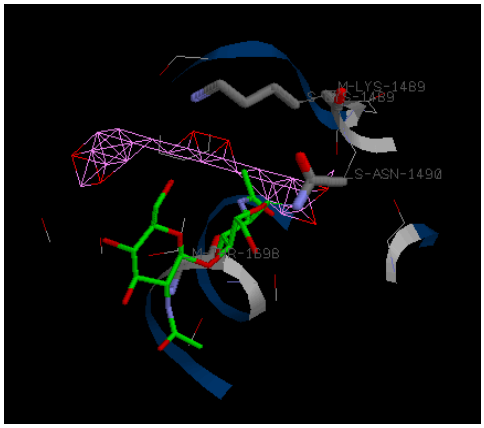


Fig. No.:4: C2

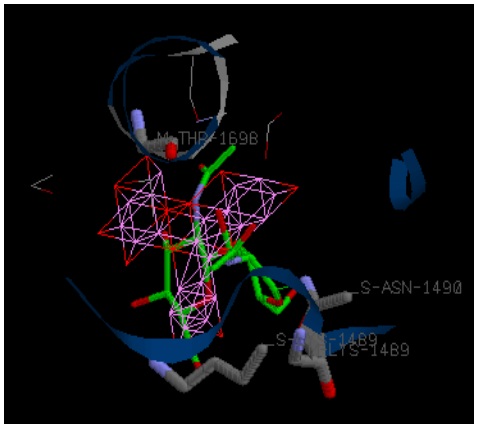


Fig. No.:5: C3

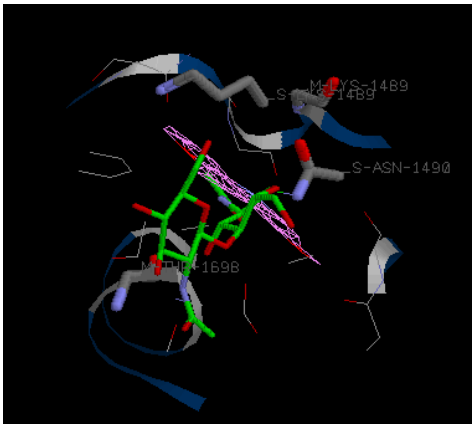


Fig. No.:6: C4

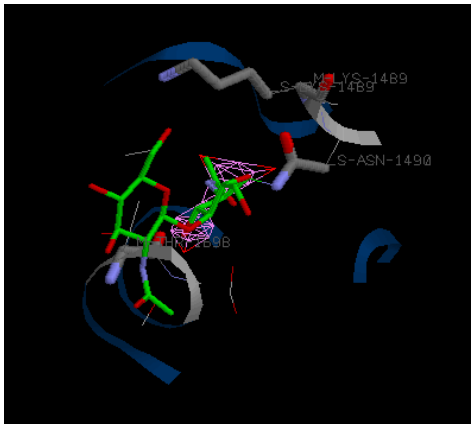


Fig. No.:7: C5

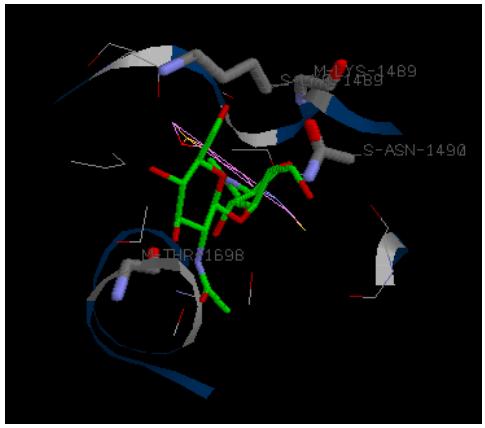


Fig.No.:8: C6

CONCLUSION

Notch signalling has an extensive role in normal development, including in adult stem cell function, and its disruption is associated with cancer, the pharmaceutical industry considers Notch to be a highly desirable therapeutic target. Using natural biotherapeutic agents it can be concluded that they can be effectively used in regulating this ubiquitous signalling system. This *In Silico* molecular docking studies is first of its kind to be done to assist the development of next generation biotherapeutics from phytochemicals.

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