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NETWORK PHARMACOLOGY AND MOLECULAR DOCKING TO ELUCIDATE THE POTENTIAL MECHANISM OF SR9009 AGAINST BREAST CANCER

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ABSTRACT

Breast Cancer (BC) is one of the most common malignant tumors. SR9009 [Ethyl 3-[[(4-chlorophenyl) methyl-[(5-nitrothiophen-2-yl) methyl] amino] methyl] pyrrolidine-1-carboxylate], a specific agonist of pyrrole derivatives has promising pharmaceutical agent and efficacy in treating several conditions including metabolic diseases such as obesity, bipolar, anxiety, depressive disorder and cancer. The goal of this study was to clarify the biological mechanism of SR9009 and develop a prediction target for SR9009 against BC using network pharmacology. We report 16 overlapping targets among 21 targets of SR9009 and 17622 known targets of breast cancer. Resulting, molecular docking analysis shows that SR9009 have affinity binding features with these hub gene targets for further consideration.

KEYWORDS: Network pharmacology, molecular docking, SR9009 targets, Breast cancer.

INTRODUCTION

Breast cancer (BC) in female is the major malignancy in the world due to its high morbidity and cancer related deaths.[1] Breast cancer was frequently diagnosed and tending to even younger ages in recent years. BC treated with conventional methods such as radiotherapy, chemotherapy and hormone therapy has limited therapeutic effects and reduce life quality of patient due to their adverse reactions.[2] REV-ERBα [also known as NR1D1(nuclear receptor subfamily 1 group D member 1)] is nuclear receptor and core component of molecular clock

system.[3] Role in direct modulation of clock and metabolic genes, REV-ERBα is first proposed as a drug target for treating sleep disorders and metabolic syndromes such as dyslipidaemia, hyperglycaemia and obesity in 2012. Bipolar, anxiety and depressive disorders and alternative medication for sleep cycle disturbance.[4] In recent years of studies uncover a broad role of REV-ERBα in pathological conditions including local inflammatory diseases, heart failure and cancers. REV-ERBα involved in regulation of circadian drug metabolism and implications in chrono pharmacology.

According to Human development Index [HDI] by the year 2040 the number of newly diagnosed breast cancers is projected to grow by over 40% to about 3 million cases every year. Similarly, deaths from BC are set out to increase more than 50% from 685,000 in 2020 to 1 million in 2040.[5] Breast cancer is the most prevalent cancer among females worldwide. WHO Global Breast cancer Initiative [GBCI] endeavours to reduce global breast cancer mortality by 2.5% per year thus avoiding 2.5 million breast cancer deaths between 2020 and 2040.[6]

Network Pharmacology is a new *in silico* drug discovery approach developed by Hopkins in 2007 to identify active compounds and putative molecular targets.[7] Network pharmacology has become a widely accessible analysis method following the increased availability of biomedical data sets during the postgenomic period, supporting the growth of the fields of systems biology and poly-pharmacology.[8] Network pharmacology and bioinformatics are emerging interdisciplinary fields involved in drug research and development. They utilize artificial intelligence as well as big data to identify active drug molecules and their molecular pathways.[9] Network pharmacology, a combination of pharmacology and pharmacodynamics, is a novel research field that allows investigators to clarify the synergistic effects and underlying multilevel interaction.

SR9009 a specific agonist of pyrrole derivatives was developed and a synthetic REV-ERB agonist is a promising pharmaceutical agent and its efficacy in treating several conditions has been studied. Network pharmacology **Figure 1** to investigate the mechanisms involved for therapeutic effects of SR9009 in Breast cancer.

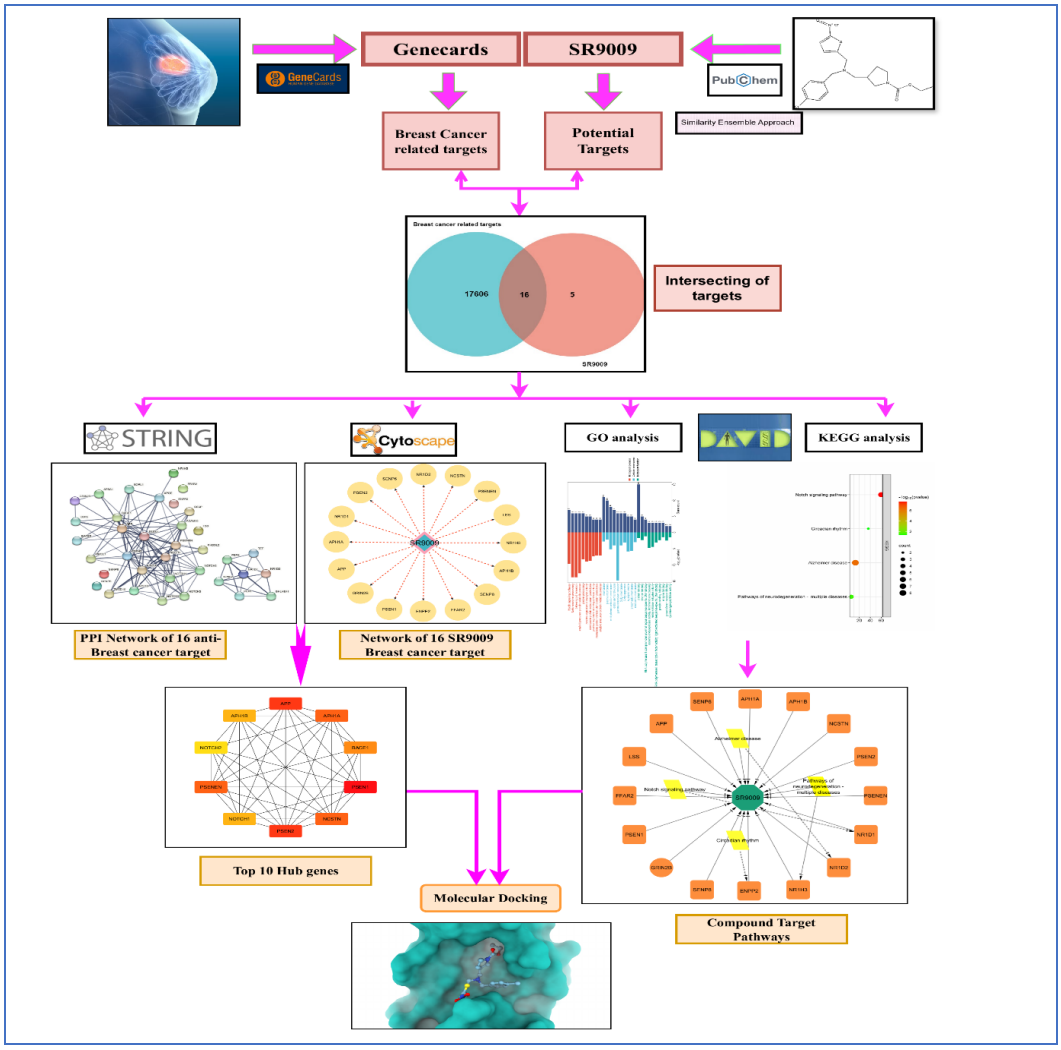

Figure 1: The workflow of the present study for predicting the mechanism of action of SR9009 in treating Breast cancer.

MATERIALS AND METHODS

PHARMACOKINETICS PROPERTIES AND TOXICITY PREDICTION

The PubChem database, which can be accessed at https://pubchem.ncbi.nlm.nih.gov[10], was used to retrieve the canonical SMILES of SR9009. SwissADME, a tool available at https://pubchem.ncbi.nlm.nih.gov[11], was used to analyze the drug likeness and physicochemical properties of SR9009, including its ADME properties. Finally, the toxicity of SR9009 was assessed using OSIRIS, a tool available at https://www.cheminfo.org/flavor/cheminformatics/Utility/Pr operty_explorer/index.html.[12]

SIMILARITY ENSEMBLE APPROACH

Similarity ensemble approach [SEA] is a 2D ligand-based similarity method that characterizes each target using its active ligand set of small molecules[13], an online platform

designed for predicting the targets of small bioactive molecules, was employed to identify potential target for SR9009. By utilizing this tool, the SMILES data of SR9009 were imported into SEA and predicted potential target were collected and analyzed.

DISEASE-TARGET PREDICTION

The potential targets were selected from Genecards [http://www.genecards.org/] **[Genecards reference]** using the keyword "Breast Cancer". GeneCards is a comprehensive database of human genes, providing integrated genetic, genomic and biological data.[14] The targets standard name was obtained from UniProtKB, specifying the organism as "Homo sapiens". The relevance score threshold for the targets in the GeneCards database was set to a minimum of 20. Furthermore, any duplicate genes were removed from the analysis.

INTERSECTION OF RELATED TARGETS

To more accurately assess the connection between breast cancer related targets and SR9009 targets, we merged the two sets of targets and created Venn diagram using an online tool from http://bioinformatics.psb.ugent.be/webtools/Venn.[15] The overlapping targets were selected for further analysis as potential therapeutic targets.

CONSTRUCTION AND ANALYSIS OF PPI (PROTEIN-PROTEIN INTERACTION) NETWORK

The potential targets of SR9009 in the context of BC, derived from Venny analysis, were introduced to the STRING 12.0 analysis platform (https://cn.string-db.org/).[16] "Multiple Proteins" was selected, species was set to high confidence (≥0.7), obtain the PPI network and save its related to TSV format information file. The TSV files were imported into Cytoscape 3.10.2, organized and plotted to obtain the PPI network graph. The Cytoscape software has been obtained by visiting Cytoscape website (https://cytoscape.org/).[17] The degree indicates the number of nodes in the network that act directly with the node and commonly used to assess node importance in networks.[18] The degree analysis was performed using CytoHubba plug-in to obtain the top 10 proteins ranked in terms of degree as the core genes.[19]

GO (GENE ONTOLOGY) AND KEGG (KYOTO ENCYCLOPEDIA OF GENES AND GENOMES) PATHWAY ANALYSIS

All potential therapeutic targets were subjected to GO and KEGG pathway enrichment analysis via the DAVID database (https://david.ncifcrf.gov/)[20] to identify the related KEGG pathways and related GO terms, including those in the biological process (BP), molecular

function (MF) and cellular component (CC) categories. DAVID is a functional enrichment database accessible through the web, enabling researchers to comprehend the bioactivity of a multitude of genes. KEGG pathways and GO terms with applicable thresholds of $p < 0.05$ were considered significant and were retained. The top 10 GO enrichments and KEGG pathways were selected for further analysis. Furthermore, Bioinformatics (http://www.bioinformatics.com.cn/)[21] was used to visualize the GO and KEGG enrichment analysis results in a bar graph of GO categories and bubble plot signalling pathways.

VERIFICATION WITH MOLECULAR DOCKING

To analyze the relationship between the key targets of SR9009 and BC targets, a molecular docking approach was employed. In this current case, ligand (SR9009) docked against top 10 hub targets. The 3D structure of ligand (SR9009) was downloaded in SDF format from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and then converted in PDB format in PYMOL software. The resolution of the crystal structure to achieve and carryout molecular modelling 2.5 to 3.0 A. The 3D structures of target proteins were obtained from the RCSB protein database (https://www.rcsb.org/).[22] Afterward, water molecules and the original ligand of the proteins were removed using PyMOL software. Pre-docking steps, active site prediction of top ten selected targets was carried out by PDB Sum database (https://www.ebi.ac.uk/thornton-srv/databases/pdbsum/).[23] Molecular docking was carried out using Auto dock 4.2.1 software based on Lamarckian Genetic Algorithm was used to determine the appropriate binding modes of ligands. Grid maps were generated by Auto Grid program. Each grid was centred at the crystal structure of the corresponding targets. A grid box with dimension of 60 Å X 60 Å X 60 Å. For all ligands, random starting positions, random orientations and torsions were used. The Docking parameters Number of Genetic Algorithm (GA) runs: 25, Population size: 150, Maximum number of generations: 27, 000 were used for this study. All the others parameters were set as defaults. The structure with the lowest binding free energy and the most cluster members was chosen for the optimum docking conformation.

TABLE 1: MOLECULAR PROPERTIES OF SR9009.

PROPERTIES	SR9009
Molecular Formula	C20H24ClN3O4S
Molecular weight	437.94
Hydrogen Bond Donor	2
Hydrogen Bond acceptor	5
Rotatable Bond	10

Topological Surface area (A)	106.84
Drug Likeness	Good
Lipinski	Yes
GI absorption	High
Clog P	2.35
Solubility log	-4.68
BBB	No
Lop Kp (skin permeation)	-5.84

TABLE 2: BINDING AFFINITY OF SR9009 AND POTENTIAL TARGET PROTEINS.

GENE NAME	PDB ID	BINDING AFFINITY (Kcal/mol)	
		SR9009	DOXORUBICIN
APH1A	5A63	-5.85	-2.91
APH1B	8OQY	-5.77	-4.14
APP	1AAP	-6.92	-6.18
BACE1	2B8L	-8.01	-5.41
PSEN1	2KR6	-6.14	-5.83
NCSTN	2N7Q	-4.96	-4.67
NOTCH1	1PB5	-5.12	-6.27
NOTCH2	2OO4	-5.29	-7.14
PSEN2	7Y5X	-5.42	-3.55
PSENEN	5A63	-5.77	-4.49

RESULTS

PHARMACOKINETIC PROPERTIES AND TOXICITY PREDICTION OF SR9009

SR9009 structural information was obtained from PubChem database were shown in **Figure 2** and related ADME data were obtained from SwissADME. **Table 1** displays the SwissADME predicted pharmacokinetic profile of SR9009. SR9009 obeys with Lipinski rule of 5 and it predicted to have good drug-likeness. The OSIRIS software was employed to assess the toxicological profile of SR9009 indicated that does not possess mutagenicity, tumorigenicity, irritant and reproductive toxicity. Furthermore, these results suggest that SR9009 is lacking of observable toxicity.

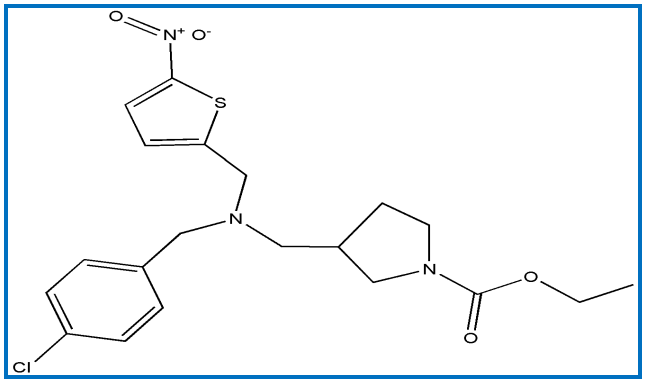

Figure 2: Structure of SR9009.

POTENTIAL TARGETS

We have collected a total of 21 SR9009 target genes from SEA database and 17622 breast cancer targets from GeneCards. Based on above data, 16 targets of SR9009 were identified against breast cancer by overlapping of 21 SR9009 associated targets and 17622 breast cancer targets shown in **Figure.**[3]

PPI NETWORK VISUALIZATION AND ANALYSIS OF SR9009

The STRING database was used to analyze the overlapped 16 potential therapeutic targets were used to identify the interactions. After that we constructed a PPI network **Figure 4**. Cytoscape software was used for the visualization of PPI network. According to the visualization, the PPI network included of 36 nodes**,** 129 edges and average node degree 7.17. After visualizing the PPI network in Cytoscape, CytoHubba - plugin was utilized to find the Hub genes. These CytoHubba – plugin offers twelve topological methods of analysis from that the degree method was selected to predict Hub genes. This degree method is based on the highest degree of connectivity between targets indicating that genes with highest degree are likely to be key targets due to their increased connectivity with other genes. Top 10 hub targets are APP, APH1A, BACE1, PSEN1, NCSTN, PSEN2, NOTCH1, PSENEN, NOTCH2 and APH1B are shown in **Figure 5**.

GO AND KEGG ENRICHMENT ANALYSIS

The GO function enrichment analysis of the 16 core targets was performed on the DAVID platform. A total of 71 GO items were obtained including 39 BP, 20 CC and 12 MF. According to GO function analysis the top ten target of BP, CC, MF categories were chosen based on $P<0.05$, as show in **Figure 6**. Target protein in the BP category were mainly involved in beta-amyloid formation, Notch receptor processing, amyloid precursor protein catabolic process, Notch signalling pathway, positive regulation of catalytic activity, membrane protein ectodomain proteolysis and positive regulation of endopeptidase activity. CC few examples are gamma-secretase complex, synaptic vesicle, presynaptic membrane, endoplasmic reticulum membrane, endoplasmic reticulum, Golgi membrane, Golgi apparatus and endosome membrane. Then finally MF such as aspartic endopeptidase activity, endopeptidase activator activity, RNA polymerase II transcription factor activity, RNA polymerase II core promoter proximal region sequence-specific DNA binding, protein binding, Zinc ion binding, enzyme binding, growth factor receptor binding and cysteine-type peptidase activity.

The potential therapeutic targets for the treatment of breast cancer against SR9009 were identified through KEGG pathway enrichment analysis. Using the DAVID database, we obtained 4 signaling pathways. We plotted the 4-signalling pathway in bubble plot graph were drawn by uploading the data to the bioinformatics platform **Figure 7**. Sorted by their P values from smallest to largest. The results Notch signaling pathway, Alzheimer disease, Pathways of neurodegeneration – multiple diseases and Circadian rhythm these pathways were significantly enriched.

CONSTRUCTION OF COMPOUND-PATHWAYS-TARGETS NETWORKS

The obtained targets of SR9009 and Breast cancer related targets were converted to standard gene names through the Uniport database. We have created a Compound-Pathway-Target network diagram to more clearly show how SR9009, pathways and targets impact depict in **Figure 8** using Cytoscape 3.10.2. Four pathways, 16 core targets with SR9009 were connected. The network confined 24 nodes and 25 edges, in which green Octagon shape represent compound (SR9009), targets were represented in orange round rectangle and pathways using yellow parallelogram shape.

MOLECULAR DOCKING

When the conformation of the ligand and receptor is stable, the possibility of action increases as the binding energy decreases. A binding energy of less than 0 kJ/mol indicates spontaneous binding between the ligand and receptor, although a binding energy of less than -5 kJ/mol suggests that the ligand and receptor bind closely. For molecular docking, ten target genes [APP, APH1A, BACE1, PSEN1, NCSTN, PSEN2, NOTCH1, PSENEN, NOTCH2 and APH1B] which were cautiously selected through a systematic examination of the PPI network. As shown in **Table 2,** among the ten targets **[APH1A, APH1B, APP, BACE1, PSEN1, NCSTN, PSEN2 and PSENEN]** showed the best interaction and strongest binding affinities towards SR9009 compared to doxorubicin. According to receptor-ligand docking theory, it is generally accepted that docking energy is inversely proportional to the binding affinity. Precisely, a more negative docking energy suggests a stronger binding affinity between the protein and the ligand.[24] Best binding affinity of SR9009 against **APH1A, APH1B, APP, BACE1, PSEN1, NCSTN, PSEN2 and PSENEN** were shown in **Figure 9**.

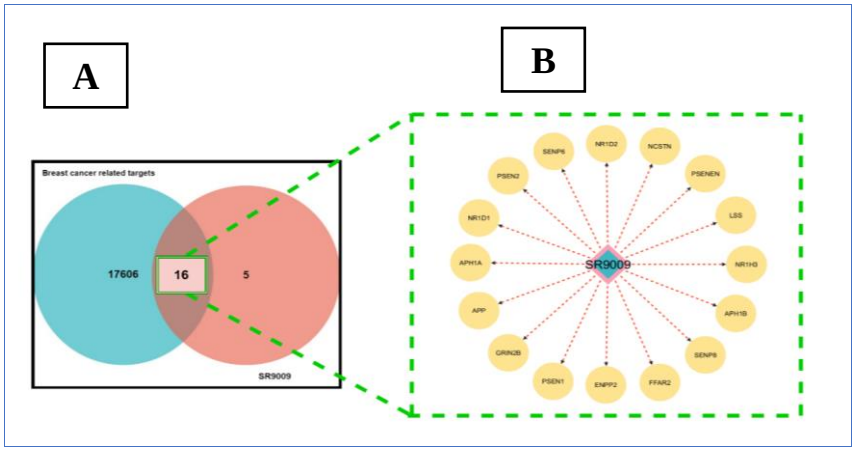

Figure 3: (A) Venn diagram of overlapping targets for SR9009 (21 targets) and BC (17622); (B) Overlapped 16 targets of SR9009 against BC.

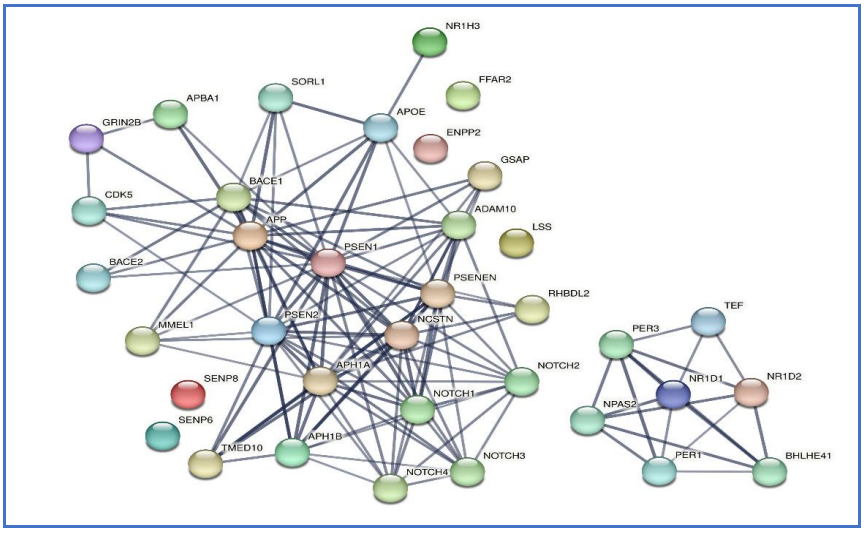

Figure 4: PPI networks of SR9009 against BC linked targets constructed by employing STRING database.

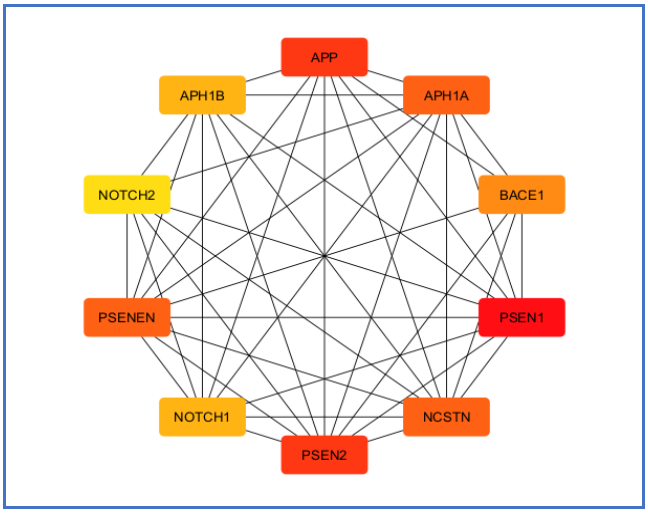

Figure 5: Top 10 core targets (Hub genes) analyzed using Cytoscape.

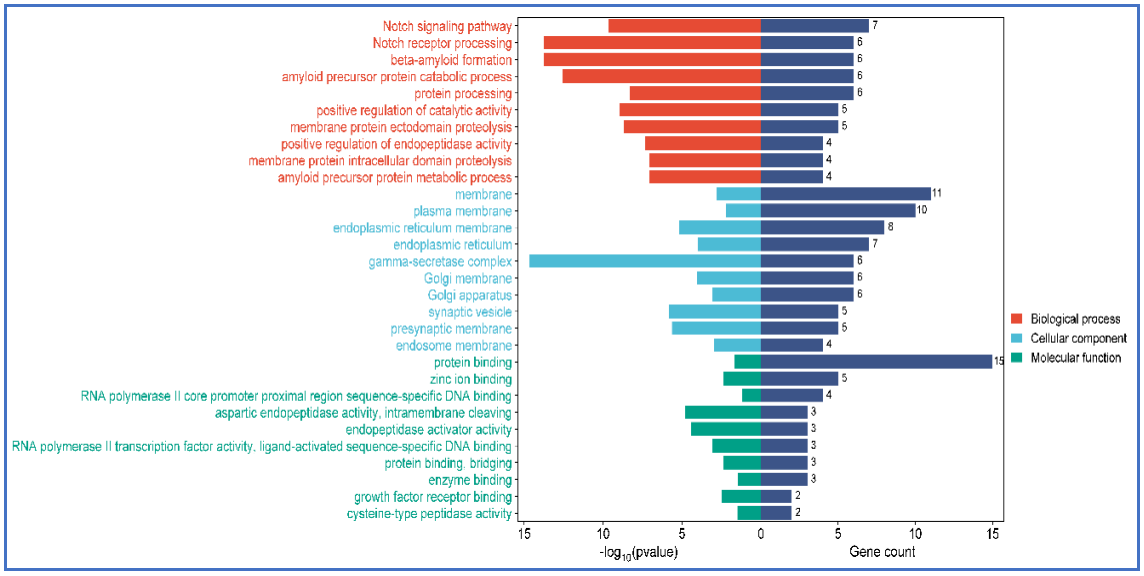

Figure 6: GO enrichment analysis of target genes. Top 10 selected according count of the gene of BP, CC & MF.

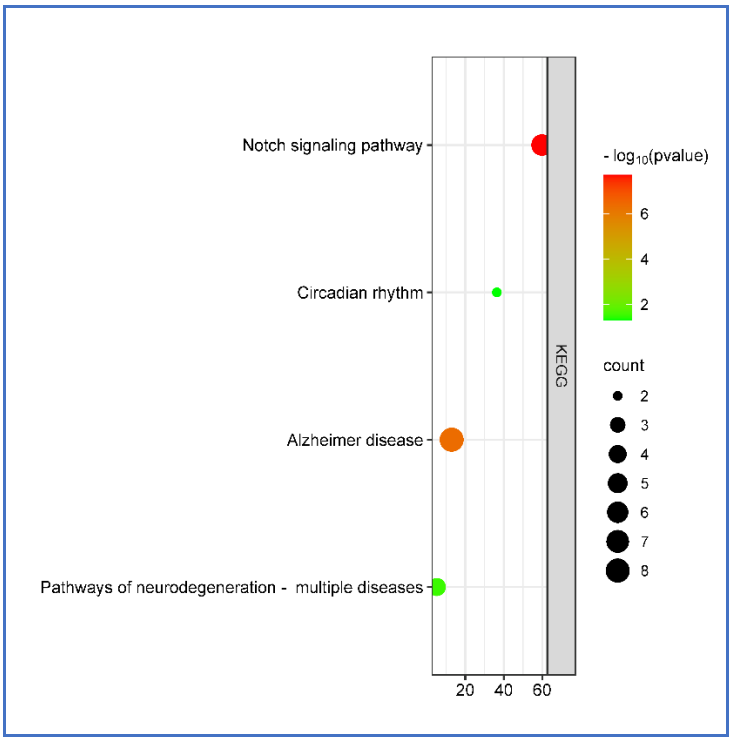

Figure 7: KEGG pathway enrichment analysis of targets gene. Y-axis represents significant pathway of target genes; X-axis show rich factor.

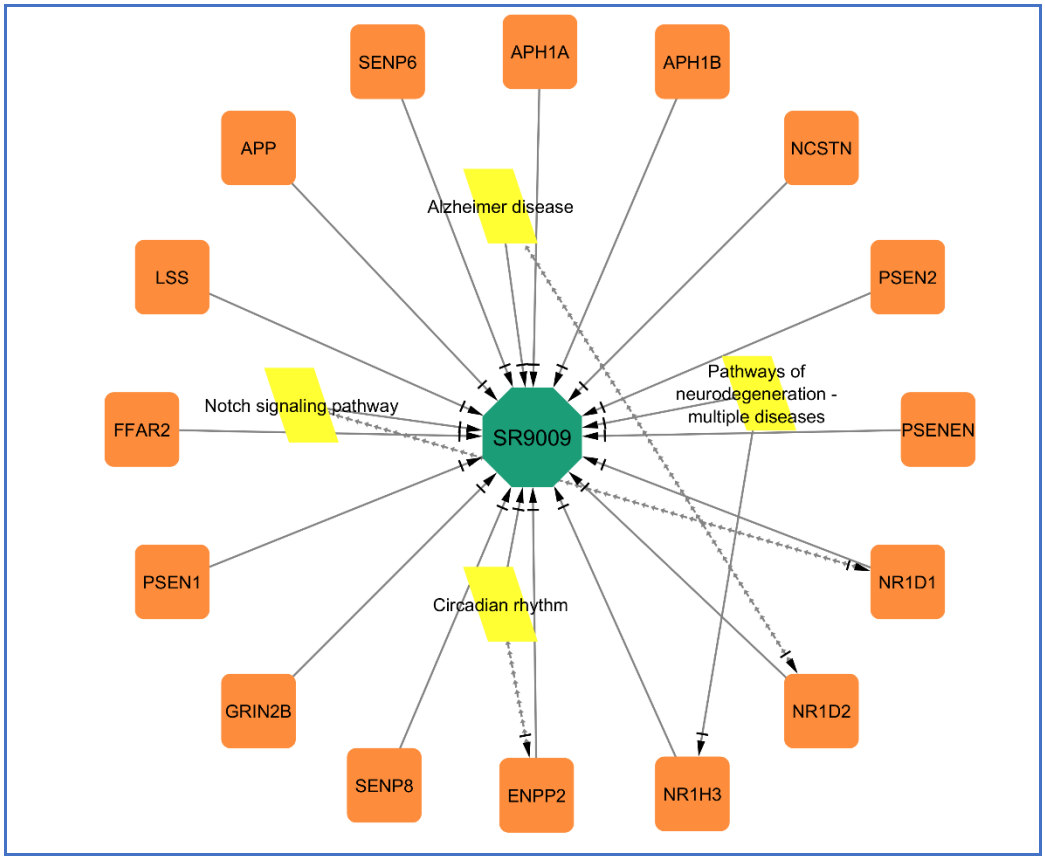

Figure 8: "SR9009-pathway-target" network diagram.

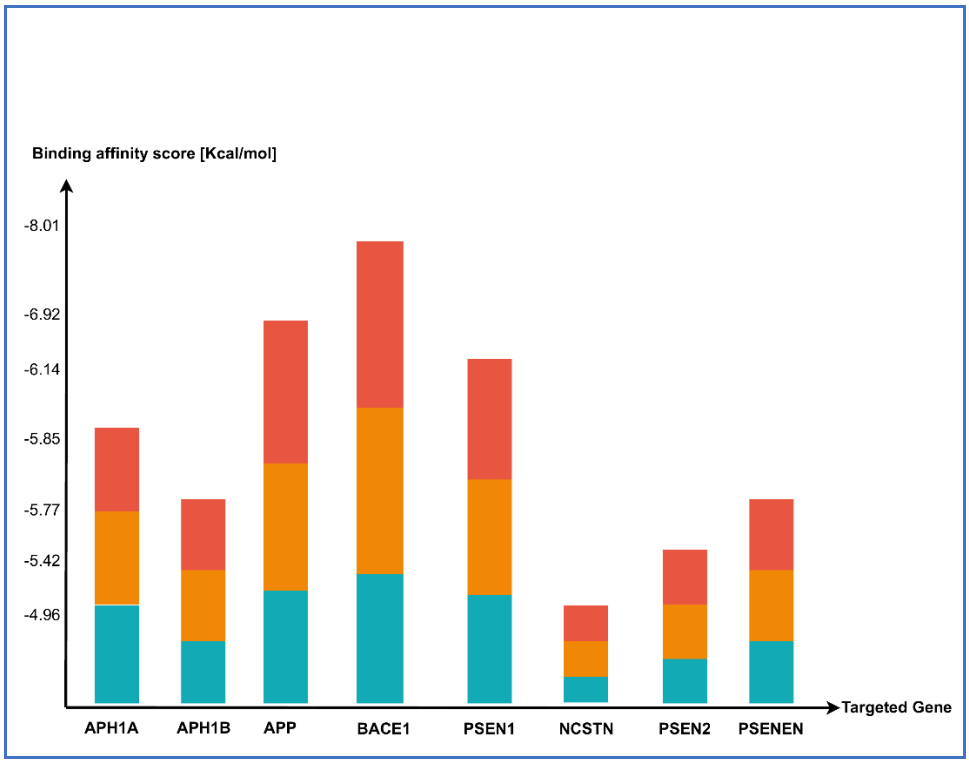

Figure 9: Best binding affinity of SR9009 against targeted gene.

DISCUSSION

Treatment of breast cancer is complex and involves a combination of different modalities including surgery, radiotherapy, chemotherapy, hormonal therapy and biological therapies delivered in diverse sequences.[25] Since that the circadian clock can effectively modulate many pathways important for tumorigenesis and progression, pharmacological regulation of circadian rhythm components may offer promising effective antitumor approaches. Single target approach opens to great promised for other type of cancers, additional aspects must be considered in order to optimize the efficacy of single target therapy we should be able to find in each patient the oncogene to which the tumor is addicted.[26] An emerging field called network pharmacology integrates system biology, pharmacology, computer sciences and information networking.[27] Network pharmacology, used in targeted therapy, uses network component analysis to characterize intricate interactions between biological systems to identify synergistic effects in cancer treatment.[28] This shift has moved us from a "one-target, one-drug" approach to a "multiple-target, multiple-component-therapeutics" approach.[29] SR9009, also known as stenabolic, is a research drug developed by Professor Thomas Burris of the Scripps Research Institute. It acts as an agonist of REV-ERB alpha, which means it increases the constitutive repression of genes regulated by REV-ERB alpha.[30] The importance of proper clock maintenance is highlighted by linkages between circadian desynchrony and a wide range of diseases, particularly cancer.[31] Previous study reported that REV-ERB alpha was involved in the antitumor effect of SR9009 in small cell lung cancer.[32] Recently, SR9009 has been reported to exert a cytotoxic effect on cancer cells, including leukemia, melanoma cells, *in vitro* and to exhibit a remarkable antitumor effect in a xenograft animal model of glioblastoma *in vivo.*[33]

In the present study, we determine the pharmacokinetic properties, toxicity prediction, potential targets and PPI network analysis of SR9009 in relation to BC. SR9009 obeys with Lipinski's rule of 5 and is predicted to have good drug-likeness. It is also free from toxicity. The study identified 16 targets of SR9009 against Breast cancer by overlapping 21 SR9009-associated targets and 17622 BC related targets. PPI network consisting of 36 nodes and 129 edges was constructed and the hub genes were identified using the CytoHubba plugin. The top ten targets were screened according to the degree and APP, APH1A, BACE1, PSEN1, NCSTN, PSEN2, NOTCH1, PSENEN, NOTCH2 and APH1B.

Constructed on GO and KEGG analyses identified that top ten targets were involved in various biological processes, molecular functions and cellular components. KEGG pathway analysis predicted 2 pathways related to Anti-breast cancer targets which significantly enriched. A drug-target-pathway network diagram was created using Cytoscape to display the interactions among SR9009, targets and pathways. Molecular docking analysis exposed those eight targets [APH1A, APH1B, APP, BACE1, PSEN1, NCSTN, PSEN2 and PSENEN] showed best binding affinity towards SR9009 compared to doxorubicin. The range of binding score of APH1A -5.85 Kcal/mol, APH1B -5.77 Kcal/mol, APP -6.92 Kcal/mol, BACE1 -8.01 Kcal/mol, PSEN1 -6.14 Kcal/mol, NCSTN -4.96 Kcal/mol, PSEN2 -5.42 Kcal/mol and PSENEN -5.77 Kcal/mol. Overall, the results based on network pharmacology and molecular docking presented in the study provide important insights into the potential anti-breast cancer mechanism of SR9009 by highlighting its ability to interact with multiple targets involved in BC development and progression. This will be serves as a future foundation of experimental research work like *In-vitro* and *In-vivo* study.

CONCLUSION

Through network pharmacology and molecular docking techniques, we have initiated and found that the SR9009 act on multiple hub targets of breast cancer. utilized network pharmacology and database mining to detect molecular targets [APH1A, APH1B, APP, BACE1, PSEN1, NCSTN, PSEN2 and PSENEN] of SR9009 against Breast cancer. On the basis of obtaining high quality therapeutic target profiles of SR9009 and BC gene sets, the therapeutic potential of SR9009 against breast cancer was systematically evaluated through a network-based approach results were found to be significant against breast cancer targets.

Conflict of Interest

The authors declare no conflicts of interest.

REFERENCES

1. Wu Q & Sharma D. Cells, 2023; 12: 1156 [PMID: 37190065]
2. Meirelles LEDF et. al., Biomedicines, 2023; 11: 275. [PMID: 36830811]
3. Everett LJ & Lazar MA. Trends Endocrinol Metab. 2014; 25: 586. [PMID: 25066191]
4. Solt LA et al. Nature, 2012; 485: 62. [PMID: 22460951]
5. Arnold M et al. Breast, 2022; 66: 15. [PMID:36084384]
6. Chaurasia M et al. Front Pharmacol., 2023; 14: 1184472. [PMID: 37576816]
7. Noor F et al. Pharmaceuticals (Basel). 2022; 15: 572. [PMID: 35631398]

8. Wang S et al. Chin. Med., 2015; 10: 19. [PMID: 26191080]
9. Xia X. Curr. Top Med. Chem., 2017; 17: 1709. [PMID: 27848897]
10. https://pubchem.ncbi.nlm.nih.gov
11. http://www.swissadme.ch
12. https://www.cheminfo.org/flavor/cheminformatics/Uti lity/Property_explorer/index.html
13. Keiser MJ et al. Nat. Biotechnol., 2007; 25: 197. [PMID: 17287757]
14. Rappaport N et al. Biomed. Eng. Online, 2017; 16: 72. [PMID: 28830434]
15. http://bioinformatics.psb.ugent.be/webtools/Venn
16. Szklarczyk D et.al. Nucleic Acids Res., 2021; 49: D605. [PMID: 33237311]
17. Reimand, J et al. Nat. Protoc., 2019; 14: 482. [PMID: 30664679]
18. Hu M et al. Sci. Rep., 2023; 13: 9569. [PMID: 37311820]
19. Chin CH et al. BMC Syst Biol., 2014; 4: S11. [PMID: 25521941]
20. Sherman BT et al., Nucleic Acids Res., 2022; 50: W216. [PMID: 35325185]
21. http://www.bioinformatics.com.cn
22. Goodsell DS et al. Protein Sci., 2020; 29: 52. [PMID:31531901]
23. https://www.ebi.ac.uk/thorntonsrv/databases/pdbsu
24. Fu S et al. BMC Complement Med. Ther., 2022; 22: 210. [PMID: 35932042]
25. Lukasiewicz S et al. Cancers (Basel). 2021; 13: 4287. [PMID: 34503097]
26. Petrelli A & Giordano S. Curr Med Chem. 2008; 15: 422. [PMID: 18288997]
27. Sakle NS et al. Sci. Rep., 2020; 10: 17217. [PMID: 33057155]
28. Kai K et al. Heliyon. 2023; 9: e17393. [PMID: 37449157]
29. Xin WA et al. Chin. J. Nat. Med., 2021; 19: 1. [PMID: 33516447]
30. https://www.benchchem.com/product/b610982
31. Liu H et al. Genes. Dis., 2023; 10: 1279. [PMID: 37397565]
32. Shen W et al. Theranostics. 2022; 10: 4466. [PMID: 32292508]
33. Sulli G et al. Nature, 2018; 553: 351. [PMID: 29320480].