Target Identification in Breast Cancer through Network Pharmacology

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Article

Target Identification in Breast Cancer through Network Pharmacology

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Abstract: In this study, we utilized the UniProt database to extract breast cancer genes Total 2658 genesin Homo sapiens are obtain. Then 166 genes are taken and after delating duplicates 158 geneswere remains. These genes were then analyzed for their biological pathways using Gene Ontology enrichment analysis through the Genecodis platform, resulting in the identification of 12 unique genes involved in disease pathways. Protein-protein interaction (PPI) network analysis was conducted using the STRING database and Cytoscape software, identifying ANLN, TREM1, LZTFL1, OXSM, PLA2G3, TAS2R13, ABCB10, ECT2, TRPC, BCAS3, PLA2G, 3, ZDHHC7 and ERBB2 as potential gene targets for breast cancer.

Keywords: breast cancer; genes; pathway analysis; protein protein interaction; degree and betweenness

Introduction

Breast cancer: breast cancer is a type of cancer that starts in the breast cells and grows out of control. It's more common in women because they are exposed to estrogen throughout their lives. It's a leading cause of cancer death in women, making up about 20-25% of all cancers in women. One in eight women will develop breast cancer during their lives. Breast cancer is the most frequent type of cancer and the second leading cause of mortality for women after lung cancer. Any breast tissue, cell, or gland has the potential to become cancerous. It can start in the ducts that produce milk or in the glandular tissues known as lobules, which produce milk. If cancer cells are not found at an early stage, there is a potential that they will damage other areas of the body and spread. Breast tumours can either be benign or malignant;benign lesions are non-cancerous cell abnormalities that cannot develop into breast cancer, whereas malignant lesions are cancerous lesions.

Network Pharmacology

In 2007, Hopkins et al. first proposed the concept "network pharmacology". This method analyzes the intervention of drugs and potential treated targets of diseases based on system biology. Network pharmacology highlights a paradigm shift from the current "one target, onedrug" strategy to a novel version of the "network target, multi-component" strategy Recently,a new technique known as polypharmacology has emerged which is able to address the limitations with current drug discovery challenges. Poly-pharmacology, also known as network pharmacology, attempts to understand drug action and interactions with multiple targets (Hopkins, 2007). It uses computational power and computer-based virtual high-throughput screening for docking studies to improve the efficiency of discovery process.

Target Identification

Target identification is the process of identifying potential targets for drug development. This process typically involves the use of computational and experimental methods to identify proteins, enzymes, receptors, or other biological molecules that are involved in the pathways of interest, and

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that could be targeted by small molecule compounds in order to treat a specific disease or condition. By identifying potential targets, researchers can develop and test small molecule compounds that are designed to interact with these targets, in order to modulate their activity and exert a therapeutic effect.

Gene Ontology

Gene Ontology is one of the main resources of biological information since it provides a specific definition of protein functions.Gene Ontology is a powerful tool in bioinformatics that helps in the standardized representation of genes and their functions across different species.

String

Protein networks have become a popular tool for analyzing and visualizing the oftenlong listsof proteins or genes obtained from proteomics and other high-throughput technologies. Oneof the most popular sources of such networks is the STRING database, which provides protein networks for more than 2000 organisms, including both physical interactions from experimental data and functional associations from curated pathways, automatic text mining, and prediction methods.

Cytoscape

cytoscape utilizes a highly reliable gene functional interaction network combined with human curated pathways derived from Reactome and other pathway databases. Biologists can use this app to uncover network and pathway patterns related to their studies, search for gene signatures from gene expression data sets, reveal pathways significantly enriched by genes in a list, and integrate multiple genomic data types into a pathway context using probabilistic graphical models.

Materials and Methods

Text Mining

The Uniprot database(https://www.uniprot.org/) was utilized to obtain genes involved in breast cancer. In which from a total of 2658 genes in homo-sapiens 158 genes are extracted and dublicate were delated. These genes were analyzed for their biological pathways and involvement in disease pathology.

GO Enrichment Analysis

Gene Ontology is a powerful tool in bioinformatics that helps in the standardized representation of genes and their functions across different species that used in analysis of cellular componants and molecular pathway .The Genecodis(https://genecodis.genyo.es/) platform was utilized in the procedure. Information of 166 genes were acquired. From these pathways 10 unique genes were sorted out as per their involvement in disease pathways and those genes were further utilized for network analysis.

PPI Network Analysis

The STRINGS database (https://string-db.org/)is used to predict protein-protein interaction networks. The Cytoscape software is utilized to visualize and analyze PPI networks in which functional enrichment data for proteins in the network is obtained and also analyzed for PPI network parameters such as degree, betweenness and compartment/tissue score. By network analysis data different potential protein targets are predicted. These protein targets are further utilized for virtual screening by molecular docking.

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Lead Identification

Lead identification is a key step in drug discovery where potential compounds with therapeutic effects are identified for further development.We utilized PubChem to explore the chemical constituents relevant to our study. We identified a total of 15 chemical constituents of green Tea, each of which plays a crucial role in our investigation. By leveraging PubChem's extensive database, we were able to comprehensively analyze the properties and characteristics of these constituents, contributing to a more thorough understanding of their potential effects and mechanisms of action within our research context.

Molecular Docking

Molecular docking is a computational technique used in the field of bioinformatics and drug discovery to predict the preferred orientation of one molecule when bound to another molecule to form a stable complex. This method helps in understanding the interactions between small molecules and proteins, which is crucial for designing new drugs or optimizing existing ones. By simulating the docking process, researchers can predict the binding affinity and mode of interaction between a ligand and receptor, aiding in the identification of potential drug candidates.

We use PDB software to download the gene structures necessary for our study.and,we utilized Pyrex software for molecular docking, a crucial step in our computational analysis. Byleveraging these tools, we were able to obtain the structural data needed for docking simulations and predict the binding interactions between our ligands and receptors accurately. This approach enabled us to gain valuable insights into the molecular mechanisms underlyingour research and facilitated the identification of potential drug candidates.

Results

UNIPROT KB: There are 158 genes are taken out of 2658 genes of breast cancer.

Go Enrichment Analysis

Go enrichment analysis was performed using Genecodis web platform. In the process top 10 pathways are selected which are associated with breast cancer. Significantly enriched genes are selectedTREM1,TRPC4,ERBB2,ANLN,ZDHHC7,LZTFL1,OXSM,PLA2G3,ECT2,TAS2R1 3,ABCB10,BCAS3,ERBB2.

PPI Network Analysis

The STRING database was used to develop the PPI network. The PPI network was visualized and analyzed using the Cytoscape app. Betweenness and Degree of centrality parametersfrom the Centiscape plugin were used to analyze the network. ANLN,TREM1,LZTFL1,OXSM,PLA2G3,TAS2R13,ABCB10,ECT2,TRPC,BCAS3,PLA2G3,ZDHHC7, ERBB2 this are the potential gene based on string analysis

Degree and betweenness Analysis

Result of target identification with degree and betweenness: Here we have identified the targets and candidate genes (Figure 5). We loaded data into Cytoscape in the ".tsv" format from the STRING EXPORT channel. Then, to evaluate each node's topological characteristics and identify the important nodes, we employed CentiScaPe, a software that computes a greater number of network characteristics. The total number of edges occurring to the node isrepresented by the node degree.

Molecular Docking

The PubMed database use for obtain chemical constituent of green tea, in that we taken 15 chemical constituent (Table 3). And download their structure from PubChem.

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Targeted protein download from PDB data base,in that 5 protein structure download out of 10 protein. Then use Pyrex for molecular docking of protein and lead ,in that 3 protein show binding with 15 leads (Table 4).

Table 1. genes of breast cancer obtain from text mining.

Entry	Gene name
Q9H2R5	KLK15
Q9H2X6	HIPK2
Q9H2X9	SLC12A5 KCC2 KIAA1176
Q9H3D4	TP63 KET P63 P73H P73L TP73L
Q9H3H5	DPAGT1 DPAGT2
Q9H3M9	ATXN3L ATX3L MJDL
Q9H3R5	CENPH ICEN35
Q9H3T3	SEMA6B SEMAN SEMAZ UNQ1907/PRO4353
Q9H3V2	MS4A5 CD20L2 TETM4
Q9H3Y6	SRMS C20orf148
Q9H467	CUEDC2 C10orf66 HOYS6
Q9H4A3	WNK1 HSN2 KDP KIAA0344 PRKWNK1
Q9H4B4	PLK3 CNK FNK PRK
Q9H4D0	CLSTN2 CS2
Q9H4H8	FAM83D C20orf129
Q9H4L2	BRCA2
Q9H4L3	BRCA2
Q9H4T2	ZSCAN16 ZNF392 ZNF435
Q9H4X1	RGCC C13orf15 RGC32
Q9H582	ZNF644 KIAA1221 ZEP2
Q9H596	DUSP21 LMWDSP21
Q9H5I1	SUV39H2 KMT1B

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Q9H5J0	ZBTB3
Q9H5V8	CDCP1 TRASK UNQ2486/PRO5773
Q9H6B1	ZNF385D ZNF659
Q9H6R7	WDCP C2orf44 PP384
Q9H6U6	BCAS3
Q9H7D7	WDR26 CDW2 MIP2 PRO0852
Q9H7L9	SUDS3 SAP45 SDS3
Q9H7N4	SCAF1 SFRS19 SRA1
Q9H7R0	ZNF442
Q9H7S9	ZNF703 ZEPPO1 ZPO1
Q9H813	PACC1 C1orf75 TMEM206
Q9H8L6	MMRN2 EMILIN3
Q9H8V3	ECT2
Q9H8Y1	VRTN C14orf115
Q9H910	JPT2 C16orf34 HN1L L11
Q9H9B1	EHMT1 EUHMTASE1 GLP KIAA1876 KMT1D
Q9HAU4	SMURF2
Q9HAU8	RNPEPL1
Q9HAW4	CLSPN
Q9HAX1	DSC3
Q9HB09	BCL2L12 BPR
Q9HB58	SP110
Q9HBL0	TNS1 TNS
Q9HBT6	CDH20 CDH7L3
Q9HBW1	LRRC4 BAG NAG14 UNQ554/PRO1111
Q9HBX8	LGR6 UNQ6427/PRO21331 VTS20631

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Q9HC10	OTOF FER1L2
Q9HC57	WFDC1 PS20
Q9HC96	CAPN10 KIAA1845
Q9HCE0	EPG5 KIAA1632
Q9HCE3	ZNF532 KIAA1629
Q9HCE6	ARHGEF10L GRINCHGEF KIAA1626
Q9HCH5	SYTL2 KIAA1597 SGA72M SLP2 SLP2A
Q9HCI5	MAGEE1 HCA1 KIAA1587
Q9HCS4	TCF7L1 TCF3
Q9HCU0	CD248 CD164L1 TEM1
Q9HCU9	BRMS1
Q9HD15	SRA1 PP7684
Q9HD64	XAGE1A GAGED2 XAGE1; XAGE1B XAGE1C XAGE1DXAGE1E
Q9HDB8	ERVK-5 ERVK5
Q9NP09	ERBB2
Q9NP58	ABCB6 MTABC3 PRP UMAT
Q9NP60	IL1RAPL2 IL1R9
Q9NP61	ARFGAP3 ARFGAP1
Q9NP99	TREM1
Q9NPC2	KCNK9 TASK3
Q9NPD5	SLCO1B3 LST2 OATP1B3 OATP8 SLC21A8
Q9NPD8	UBE2T HSPC150 PIG50
Q9NPG8	ZDHHC4 ZNF374 DC1 UNQ5787/PRO19576
Q9NPY3	CD93 C1QR1 MXRA4
Q9NQ31	AKIP1 BCA3 C11orf17
Q9NQ48	LZTFL1

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Q9NQ66	PLCB1 KIAA0581
Q9NQ88	TIGAR C12orf5
Q9NQB0	TCF7L2 TCF4
Q9NQC3	RTN4 KIAA0886 NOGO My043 SP1507
Q9NQG5	RPRD1B C20orf77 CREPT
Q9NQR3	BRCA1
Q9NQU5	PAK6 PAK5
Q9NQW6	ANLN
Q9NQX1	PRDM5 PFM2
Q9NR12	PDLIM7 ENIGMA
Q9NR30	DDX21
Q9NR80	ARHGEF4 KIAA1112
Q9NR82	KCNQ5
Q9NR96	TLR9 UNQ5798/PRO19605
Q9NRA2	SLC17A5
Q9NRC1	ST7 FAM4A1 HELG RAY1
Q9NRD0	FBXO8 FBS FBX8 DC10 UNQ1877/PRO4320
Q9NRH2	SNRK KIAA0096 SNFRK
Q9NRJ1	C8orf17
Q9NRK6	ABCB10
Q9NRM2	ZNF277 NRIF4 ZNF277P
Q9NRN9	METTL5 DC3 HSPC133
Q9NRP0	OSTC DC2 HDCMD45P HSPC307
Q9NRP7	STK36 KIAA1278
Q9NRY4	ARHGAP35 GRF1 GRLF1 KIAA1722 P190A p190ARHOGAP
Q9NS23	RASSF1 RDA32

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Q9NS39	ADARB2 ADAR3 RED2
Q9NS71	GKN1 AMP18 CA11 UNQ489/PRO1005
Q9NS87	KIF15 KLP2 KNSL7
Q9NSC7	ST6GALNAC1 SIAT7A UNQ543/PRO848
Q9NTF0	DKFZp727E011
Q9NTG1	PKDREJ
Q9NTK1	DEPP1 C10orf10 DEPP FIG
Q9NTK5	OLA1 GTPBP9 PRO2455 PTD004
Q9NTM9	CUTC CGI-32
Q9NTW7	ZFP64 ZNF338
Q9NTX7	RNF146
Q9NTX9	FAM217B C20orf177
Q9NU02	ANKEF1 ANKRD5
Q9NUM3	SLC39A9 ZIP9 UNQ714/PRO1377
Q9NUQ7	UFSP2 C4orf20
Q9NUT2	ABCB8 MABC1 MITOSUR
Q9NV12	TMEM140
Q9NV23	OLAH THEDC1
Q9NV64	TMEM39A SUSR2
Q9NVA1	UQCC1 BZFB C20orf44 UQCC
Q9NVD3	SETD4 C21orf18 C21orf27
Q9NVE7	PANK4
Q9NVM9	INTS13 ASUN C12orf11 GCT1
Q9NVP1	DDX18 cPERP-D
Q9NVW2	RLIM RNF12
Q9NVX2	NLE1 HUSSY-07

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Q9NW75	GPATCH2 GPATC2
Q9NWB6	ARGLU1
Q9NWK9	ZNHIT6 BCD1 C1orf181
Q9NWM0	SMOX C20orf16 SMO UNQ3039/PRO9854
Q9NWU1	OXSM
Q9NX61	TMEM161A UNQ582/PRO1152
Q9NXF8	ZDHHC7
Q9NXL2	ARHGEF38
Q9NY72	SCN3B KIAA1158
Q9NY74	ETAA1 ETAA16
Q9NYC9	DNAH9 DNAH17L DNEL1 KIAA0357
Q9NYF0	DACT1 DPR1 HNG3
Q9NYV9	TAS2R13
Q9NZ20	PLA2G3
Q9NZ52	GGA3 KIAA0154
Q9NZC7	WWOX FOR SDR41C1 WOX1
Q9NZC9	SMARCAL1 HARP
Q9NZJ4	SACS KIAA0730
Q9NZJ5	EIF2AK3 PEK PERK
Q9NZL6	RGL1 KIAA0959 RGL
Q9NZP6	NPAP1 C15orf2
Q9P032	NDUFAF4 C6orf66 HRPAP20 HSPC125 My013
Q9P0G3	KLK14 KLKL6
Q9P253	VPS18 KIAA1475
Q9P260	RELCH KIAA1468
Q9P283	SEMA5B KIAA1445 SEMAG UNQ5867/PRO34001

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Q9P287	BCCIP TOK1
Q9P2J8	ZNF624 KIAA1349
Q9P2U8	SLC17A6 DNPI VGLUT2
Q9T3Q5	ND2 NADH2
Q9UBB6	NCDN KIAA0607
Q9UBF1	MAGEC2 HCA587 MAGEE1
Q9UBF9	MYOT TTID
Q9UBK9	UXT HSPC024
Q9UBN4	TRPC4
Q9UBN7	HDAC6 KIAA0901 JM21
Q9UBP0	SPAST ADPSP FSP2 KIAA1083 SPG4
Q9UBS9	SUCO C1orf9 CH1 OPT SLP1

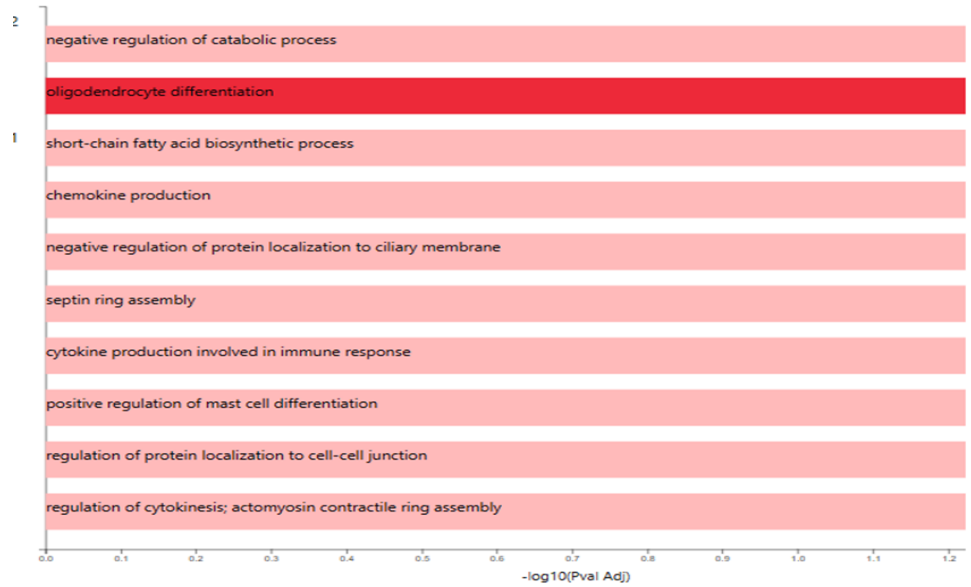

Figure 1. GO enrichment analysis chart bar length signifies -log10(pval Ad)and red colour intensity signifies number of input genes involved in pathway.

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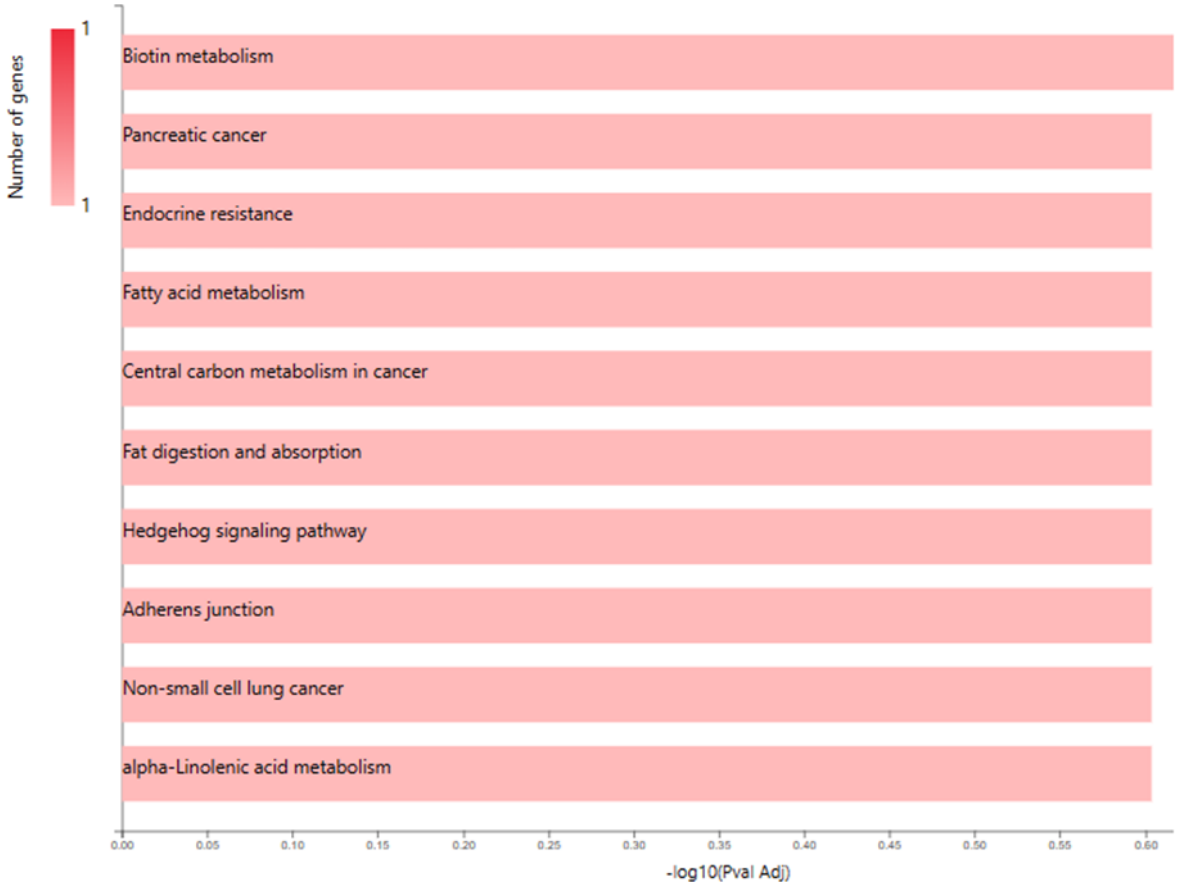

Figure 2. KEGG enrichment analysis chart bar length signifies -log10(pvalAdj) and red colour intensity signifies number of input genes involved in pathway.

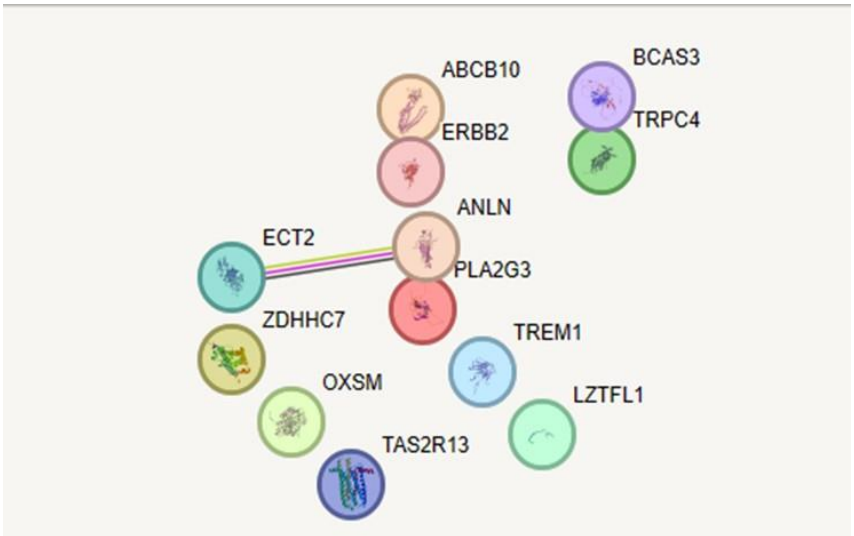

Figure 3. Protein protein interaction in string database.network nodes represent proteins,different coloured edges represent protein-protein interaction.

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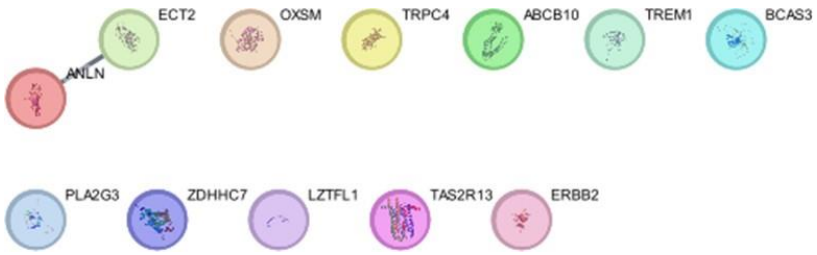

Figure 4. The protein-protein interaction network of genes and identification of candidate genes, produced using Cytoscape.

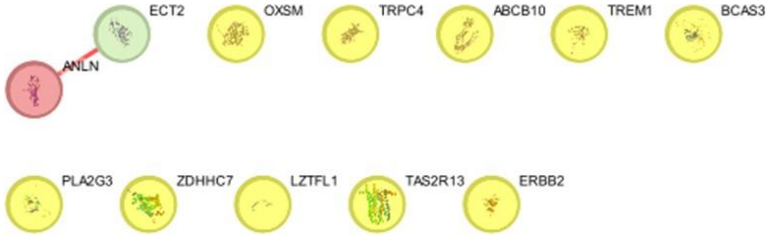

Figure 5. The degree and betweenness of the protein are produce by using centiscape.

Table 2. Degree and betweenness obtain using centiscape.

GENES	DEGREE	BETWEENES
ERBB2	0	0
LZTFL1	0	0
ZDHHC7	0	0
PLA2G3	0	0
BCAS3	0	0
TREM1	0	0
ABCB10	0	0
ECT2	1	0
TRPC4	0	0
OXSM	0	0
ANLN	1	0

Table 3. Chemical constituent of green tea obtain from PubChem.

Epigallocatechin	Gallocatechol
Epicatechin gallate	Gallic acid
Catechin	Theaflavin
Theanine	Chlorogenic acid
Theobromine	Epicatechin 3 gallate
Catechol	epigallocatechin
Gallocatechin	linolool

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Quinic acid

Table 4. Binding Affinity between ligand and protein.

Ligand	Binding Affinity	Ligand	BindingAffinity
ABCB10_catechin	-6.6	ERBB2_catechin	-7.5
ABCB10_CATECHOL	-4.4	ERBB2_CATECHOL	-5.2
ABCB10_chlorogenic_acid	-6.4	ERBB2_chlorogenic_acid	-7
ABCB10_epicatechin_3_gallate	-7.3	ERBB2_epicatechin_3_gallate	-8.8
ABCB10_epicatechin_gallate	-7.2	ERBB2_epicatechin_gallate	-7.6
ABCB10_epigallocatechin	-7.2	ERBB2_epigallocatechin	-8.9
ABCB10_epigallocatechol	-6.7	ERBB2_epigallocatechol	-7.5
ABCB10_gallic_acid	-5	ERBB2_gallic_acid	-6.3
ABCB10_gallocatechin	-6.8	ERBB2_gallocatechin	-7.2
ABCB10_gallocatechol	-6.8	ERBB2_gallocatechol	-7.2
ABCB10_linalool	-5	ERBB2_linalool	-5
ABCB10_quinic_acid	-4.9	ERBB2_quinic_acid	-5.9
ABCB10_theaflavin	-7.9	ERBB2_theaflavin	-9.4
ABCB10_theanine	-4.4	ERBB2_theanine	-4.6
		ERBB2_theobromine	-5.3

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ABCB10_theobromine	-5.1		
TREM1_catechin	-6.5	TREM1_linalool	-4.3
TREM1_CATECHOL	-5.2	TREM1_quinic_acid	-5.1
TREM1_chlorogenic_acid	-7.1	TREM1_theaflavin	-7.7
TREM1_epicatechin_3_gallate	-7.3	TREM1_theanine	-4.4
TREM1_epicatechin_gallate	-6.9	TREM1_theobromine	-4.6
TREM1_epigallocatechin	-6.9	TREM1_gallocatechin	-6.6
TREM1_epigallocatechol	-6.5	TREM1_gallocatechol	-6.6
TREM1_gallic_acid	-5.6		

Discussion

Breast cancer has a high rate of metastasis and a fatality rate of over 70% when it spreads. Itis well acknowledged that surgical excision is the primary treatment for most cases of breast cancer.After doing a gene set enrichment analysis, we were able to identify 158 target genes in this study. The carcinogenic process's genetic modifications affect how cells function, enabling self-sufficiency in growth signals, insensitivity to antigrowth signals, escape from apoptosis, infinite replicative potential, invasion, angiogenesis, and metastasis. These changesare consistent with the enriched biological processes—such as "cell differentiation," "cell division," "cell adhesion," and "signal transduction"—that were found using GeneCodisanalysis (Table 1). The appropriate genes are then exported to the STRING database to check and analyse the protein-protein interaction along with the study of different types of nodes present. The same genes are as well transferred to the Cytoscape to visualize the interaction of targets more flexibly. With the targeted gene we came across the degree and betweenness of the genes, which helped us to imply the candidate genes for the further analysis with drugs.

Conclusion

The genes that have shown the targeted interaction are: ECT1 and ANLN.

From the above network pharmacology with various analytical tools, we came to the conclusion that, with the incidence of breast cancer on the rise and patient expectations rising in recent years, selecting an appropriate treatment to maximize preservation of function and minimize the risk of metastasis and recurrence remains challenging. In the clinic, surgical excision is frequently considered the best course of action for treating breast cancer. Non-surgical techniques like photodynamic therapy (PDT), radiation therapy, cryotherapy, and chemotherapy are commonly used to treat late-stage breast cancer. However, research on pharmaceutical therapy is still lacking, and more studies are needed to help develop novel therapeutic strategies.

Even though the efficacy of the currently available drug therapies is limited, and the discovery of new drug therapies using traditional methods is likely to take a long time, drug repositioning may speed up the process of discovering additional conditions that existing drugs could treat more effectively and potentially at a lower cost. This study aimed to investigate new drug therapies for breast cancer by means of computational methods including text mining, biological process and pathway analysis, protein-protein interaction (PPI) analysis to mine public databases, and bioinformatics tools to systematically identify interaction networks between drugs and gene targets.

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We were able to use data analytical techniques to look at the characteristics of possible genes in order to select a medication.

With the help of these targeted candidate genes, we can further take the analysis towards the gene-drug data interpretation and find the genes that can be used as a biomarker in correspondence with the drugs compounded for the breast cancer.

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