Network Pharmacology of Ar-Turmerone

Ritesh Jagtap, Rutuja Jagdale, Snehal Koli
Padmini College of Pharmacy, Dighanchi

Abstract- Network pharmacology is a systems-level approach to drug discovery that transcends the traditional "one drug–one target" paradigm by exploring multi-target interactions among genes, proteins, and pathways. This study leverages network pharmacology integrated with molecular docking to evaluate the therapeutic potential of Ar-turmerone, a bioactive compound derived from *Curcuma longa*, against cancer-related targets.

Using SMILES input, SwissADME and SwissTargetPrediction tools were employed to identify pharmacokinetic properties and molecular targets of Ar-turmerone. Disease-associated genes were retrieved from DisGeNET, Malacards, and OMIM databases. Comparative analysis through Venny highlighted five overlapping genes: ESR1, BRCA2, PIK3CA, TP53, and CDH1. Protein-protein interaction (PPI) networks were constructed using STRING and further analyzed in Cytoscape using centrality measures to determine key regulatory nodes.

Pathway enrichment via Reactome revealed that Ar-turmerone potentially modulates two critical pathways: Constitutive PI3K/AKT signaling (associated with PIK3CA mutations in cancers) and extra-nuclear estrogen signaling (mediated by ESR1). These pathways are essential in cancer progression, cell proliferation, apoptosis resistance, and metastasis.

The integration of computational and systems biology tools in this study underlines the promising multi-targeted therapeutic potential of Ar-turmerone and demonstrates the value of network pharmacology in natural product-based drug discovery.

Key Point- Network Pharmacology, gene,Ar-turmerone

INTRODUCTION OF NETWORK PHARMACOLOGY-

Network pharmacology is an innovative field that provides a systems-level understanding of drug actions by analyzing the complex interactions among biological components. Instead of focusing on a single target, as in traditional pharmacology, this approach investigates how drugs affect multiple interconnected elements such as genes, proteins, and metabolic pathways. This broader perspective is particularly useful for uncovering the mechanisms of multi-target drugs and identifying opportunities for drug repurposing.

The discipline integrates principles from systems biology, genomics, and proteomics. It applies a combination of computational tools and experimental techniques, including in vitro and in vivo studies, to explore drug-disease relationships and discover new therapeutic pathways.

Key computational techniques used in network pharmacology include:

- Network topology analysis
- Simulation of random networks
- Comparative network studies
- Clustering methods
- Advanced visualization tools

Historical Development

The foundation of network pharmacology was laid in 1999 when Professor Shao Li explored how Traditional Chinese Medicine (TCM) interacts with biomolecular networks. He proposed that herbal formulations might influence disease-related gene networks through complex, multi-level effects. In 2007, Li and his team used bioinformatics to build the first molecular network model related to TCM's Cold/Hot syndrome, providing evidence of the systemic regulatory role of herbal formulas.

Also in 2007, Dr. Andrew L. Hopkins from the University of Dundee formally introduced the term ″Network Pharmacology,″ promoting it as a new paradigm in drug discovery. His work emphasized moving away from the “one drug–one target” model toward a more holistic, network-based approach.

By 2009, researchers like Pan Jiahu had begun applying network pharmacology in modern drug discovery, especially in alignment with TCM principles. In the same year, Li proposed an integrated model combining phenotypic, biological, and TCM-related networks. Later, in 2011, he introduced the concept of “network targets,” which allowed for the prediction of synergistic drug combinations.

To promote consistency and reliability in this emerging field, Li's team published a global guideline in 2021 titled ″Guidelines for Evaluation Methods in Network Pharmacology.″ This established a standardized methodology for assessing research quality and data integrity.

Fundamentals of Network Pharmacology

Network pharmacology integrates systems biology, cheminformatics, bioinformatics, and pharmacology to explore drug-target interactions and disease mechanisms. The field leverages computational modeling and high-throughput screening to understand how bioactive compounds influence various biological networks. (1)

Challenges and Future Prospects

Despite its growing success, network pharmacology and molecular modeling still face several limitations:

- Data Integration: The combination of diverse biological datasets (genomic, proteomic, metabolomic) poses a significant computational challenge.
- Experimental Validation: Predictions made through computational tools must be confirmed with rigorous lab-based studies.
- Off-Target Effects: Unanticipated drug interactions within complex biological networks remain difficult to predict.
- Limitations of Algorithms: Current docking and modeling algorithms may not always provide accurate predictions and require continual refinement.

Looking ahead, the integration of artificial intelligence (AI) and machine learning (ML) offers promising enhancements to predictive modeling in drug discovery. Additionally, advances in multi-omics technologies (e.g., transcriptomics, metabolomics) are expected to enrich the network pharmacology framework, leading to more personalized and efficient therapeutic strategies. (2)

Molecular Introduction-

Molecule name – Ar-turmerone

Trade names – Not commercially standardized; found in turmeric oil formulations

Bioavailability – Low (enhanced via nanoformulations or intranasal delivery)

Protein binding – Not well established; under investigation

Metabolism – Hepatic metabolism; cytochrome P450 enzymes (likely CYP3A4) involved

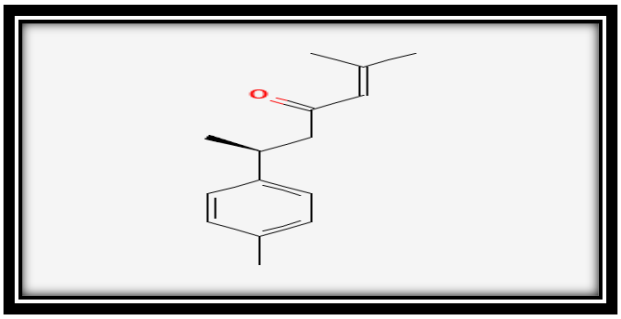
Elimination half-life – Not precisely defined; varies with delivery system

Excretion – Presumed fecal and biliary routes (similar to other lipophilic sesquiterpenes)

IUPAC Name – (6S)-6-Isopropenyl-4-methyl-3-cyclohexen-1-one

Research Objective:

This article aims to research and update the mechanisms of action and therapeutic applications of Ar-turmerone in a range of neuroinflammatory and neurodegenerative disorders, emphasizing its neurogenic potential, anti-inflammatory properties, and drug-target network identified through computational pharmacology.



Mechanism of Action (MOA) of Ar-turmerone:

1. Neurogenesis Promotion:
   - Stimulates proliferation and differentiation of neural stem cells (NSCs), particularly in the subventricular zone (SVZ) and hippocampus.
   - Activates PI3K/Akt and ERK1/2 signaling pathways, promoting cell survival and neuroregeneration.
2. Anti-inflammatory Effects:
   - Inhibits microglial activation, reducing the production of pro-inflammatory cytokines like IL-1β, IL-6, TNF-α.
   - Modulates NF-κB signaling pathway to suppress neuroinflammation.
3. Antioxidant Activity:

- Scavenges free radicals and enhances endogenous antioxidant enzymes like SOD, catalase, and glutathione peroxidase.

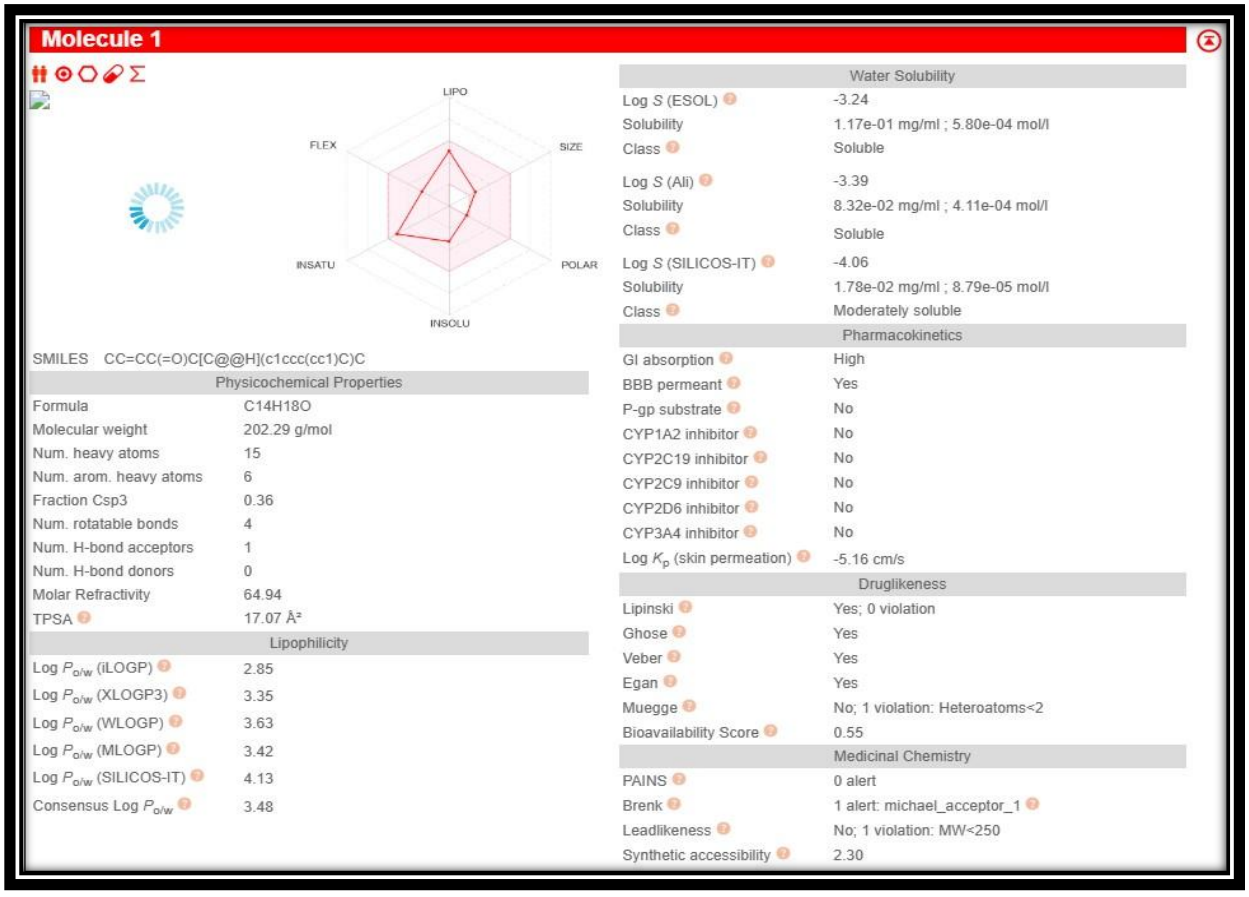
4. Modulation of Cell Death Pathways:
   - Inhibits apoptosis by regulating Bcl-2 family proteins and caspase pathways.
5. Lipid and Membrane Interaction:
   - Interacts with cell membranes due to its lipophilic structure, facilitating BBB penetration and intracellular action.

Medicinal use-

1. Neurodegenerative Diseases:
2. Alzheimer's Disease: Promotes neurogenesis and reduces neuroinflammation.
3. Parkinson's Disease: Protects dopaminergic neurons and inhibits microglial toxicity.
4. Brain Injury & Stroke Recovery:
5. Enhances neural regeneration and cognitive recovery post-injury.
6. Epilepsy:
7. Demonstrates anticonvulsant effects in animal models.
8. Anti-cancer (under research):
9. Shows potential to inhibit proliferation of certain cancer cells (e.g., glioblastoma) through apoptosis induction.
10. Mood and Cognitive Enhancement:
11. Possible nootropic and anxiolytic effects due to neurogenesis stimulation and anti-inflammatory activity. (3)

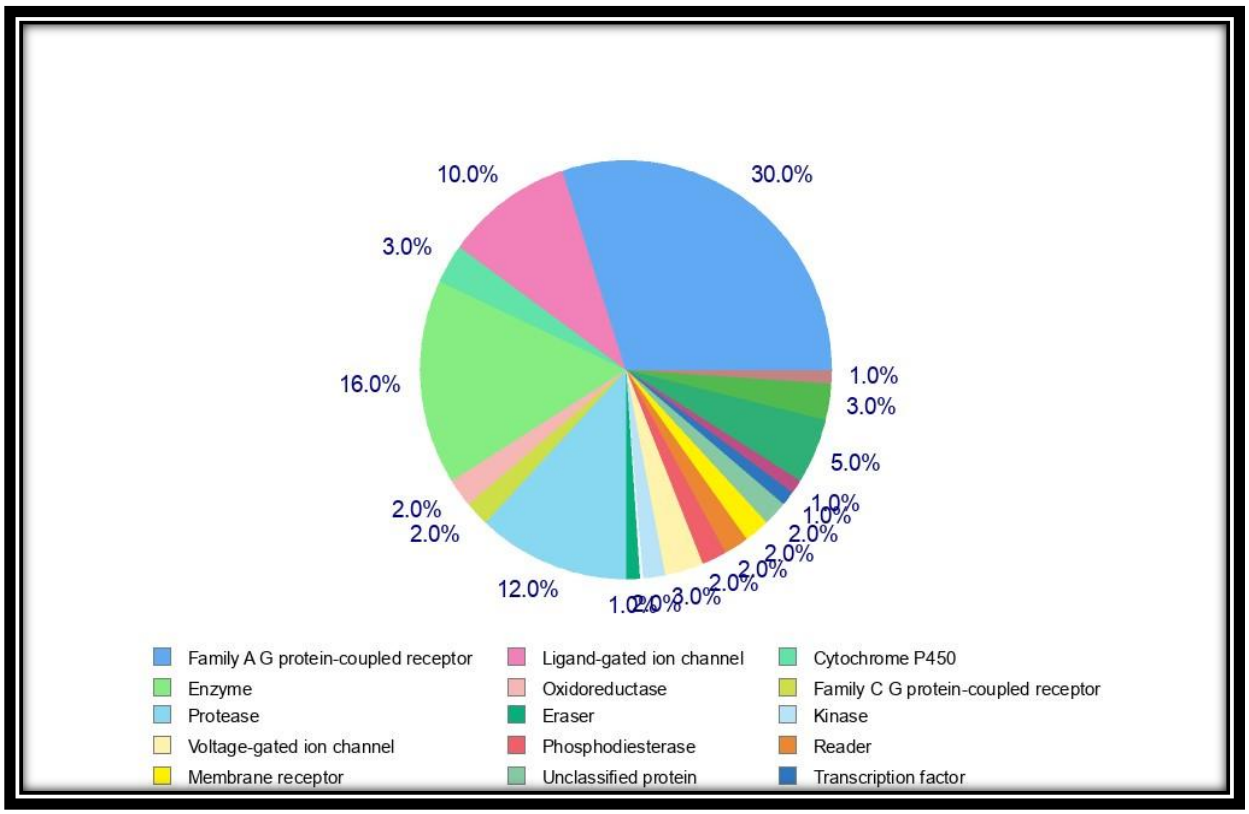
MATERIAL AND METHOD

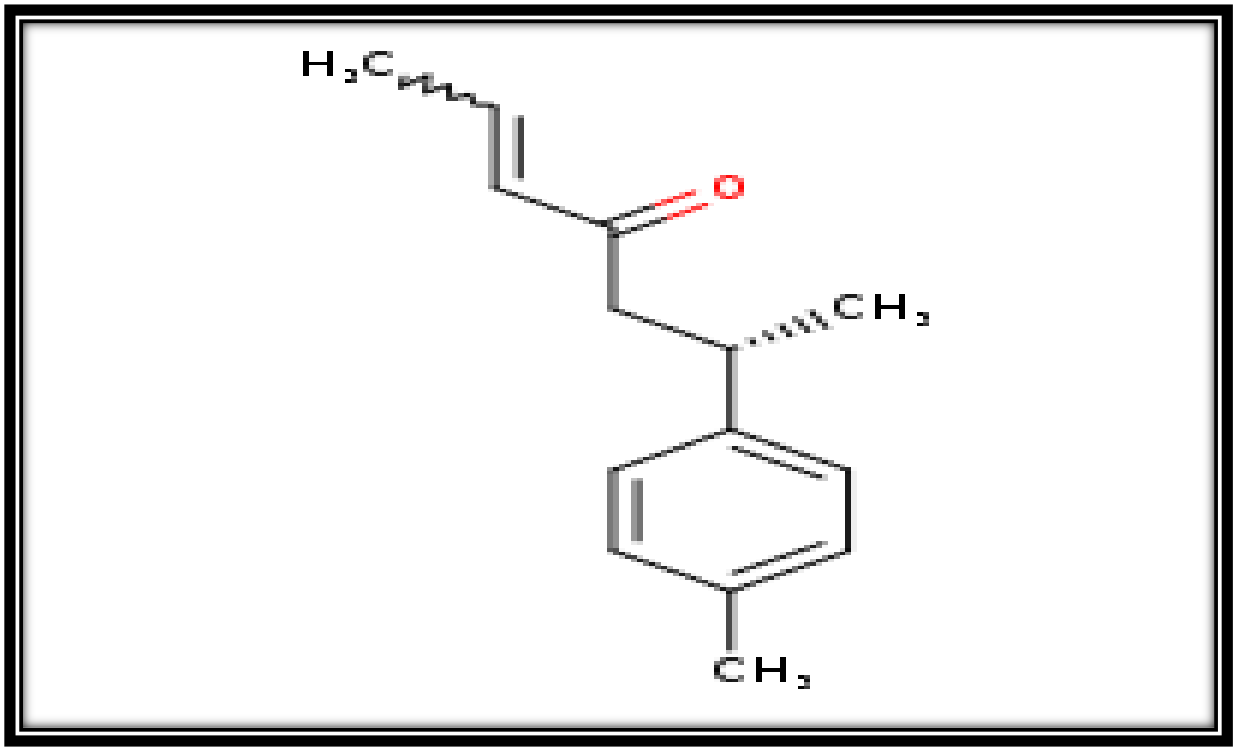
1) Selection of Phytochemical-
SMILES of Ar-turmerone-
CC1=CC=C(C=C1)[C@@H](C)CC(=O)C=C(C



2. Selection of Target Identification:

SWISS TARGET



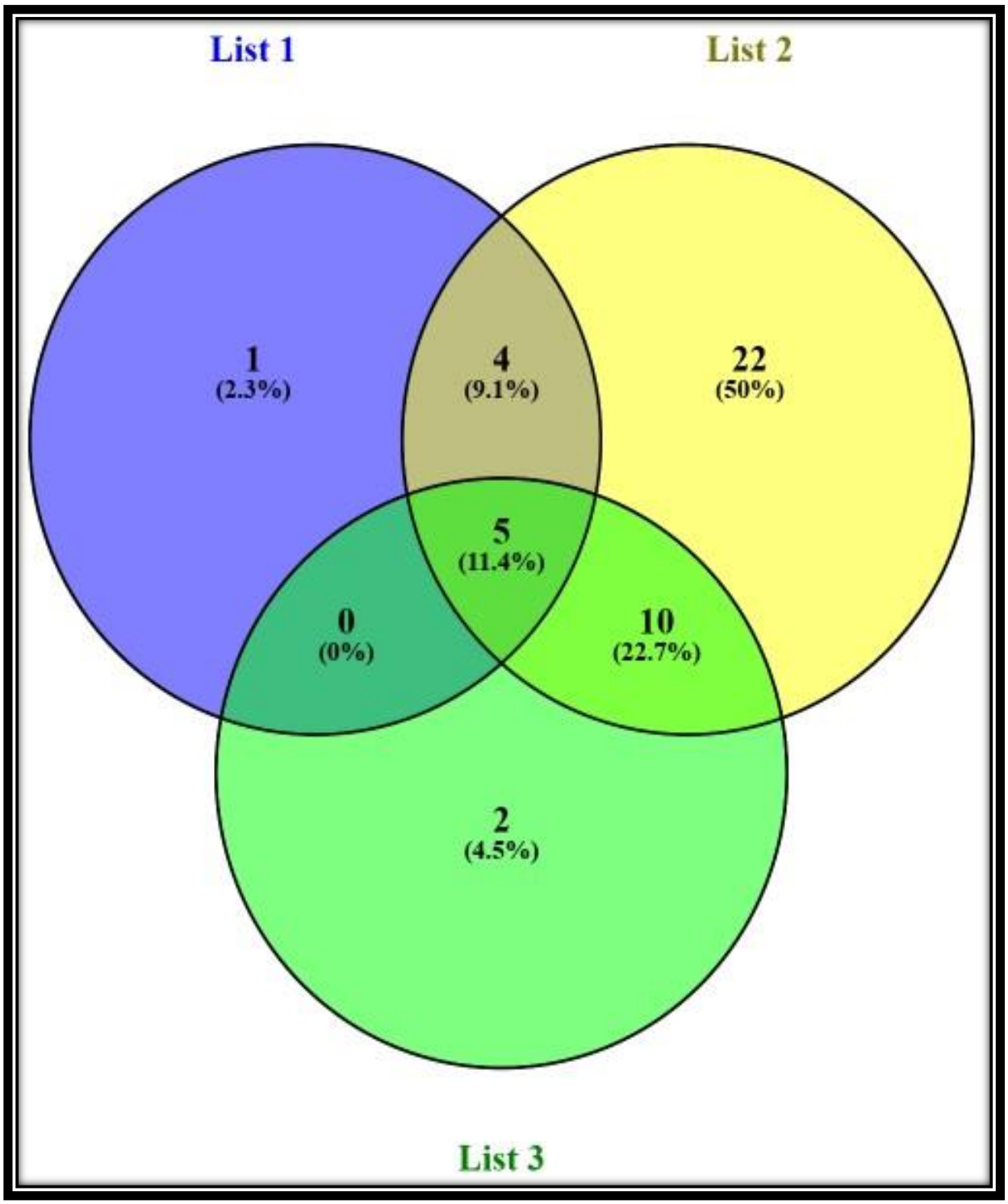


3. disease Gene-

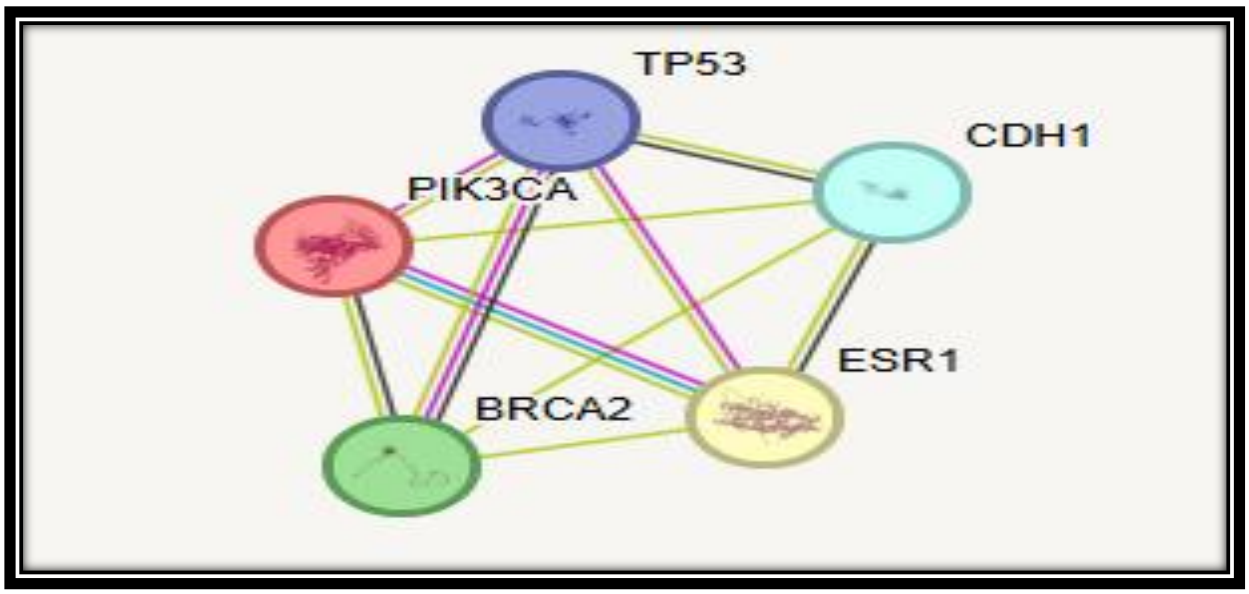
DISGENET	Malacard	OMIM
ESR1	BRCA2	RAD54L
BRCA2	RAD51	CASP8
BRCA1	BRIP1	BARD1
PIK3CA	PIK3CA	PIK3CA
TP53	AKT1	HMMR
CDH1	ATM	NQO2
PTEN	ESR1	ESR1
ATM	BARD1	RB1CC1
CHEK2	CDH1	BRCA2
FGFR2	PPM1D	XRCC3
	TP53	AKT1
	KRAS	RAD51
	BRCA1	CDH1
	CHEK2	TP53
	NBN	PHB1
	RAD54L	PPM1D
	PHB1	BRIP
	XRCC3	
	CASP8	
	HMMR	
	RB1CC1	
	ERBB2	
	SLC22A18	
	PTEN	
	PALB2	
	APC	
	RAD50	
	MSH6	
	MRE11	
	RAD51D	
	PMS2	
	FANCC	
	MSH2	
	MUTYH	
	MLH1	
	RAD51C	
	BLM	
	FANCM	
	IL7R	
	DCTN5	
	CDC73	

4.Selection Of Common Genes-
VENNY-
1.ESR1
2.BRCA2

3.PIK3CA
4.TP53
5.CDH1



1) PPI intraction and ranking-
STRING DATA-



CYTOSCAPE- Centrality measure

Results Panel

Result 4 ▾

Result List(5 in total)

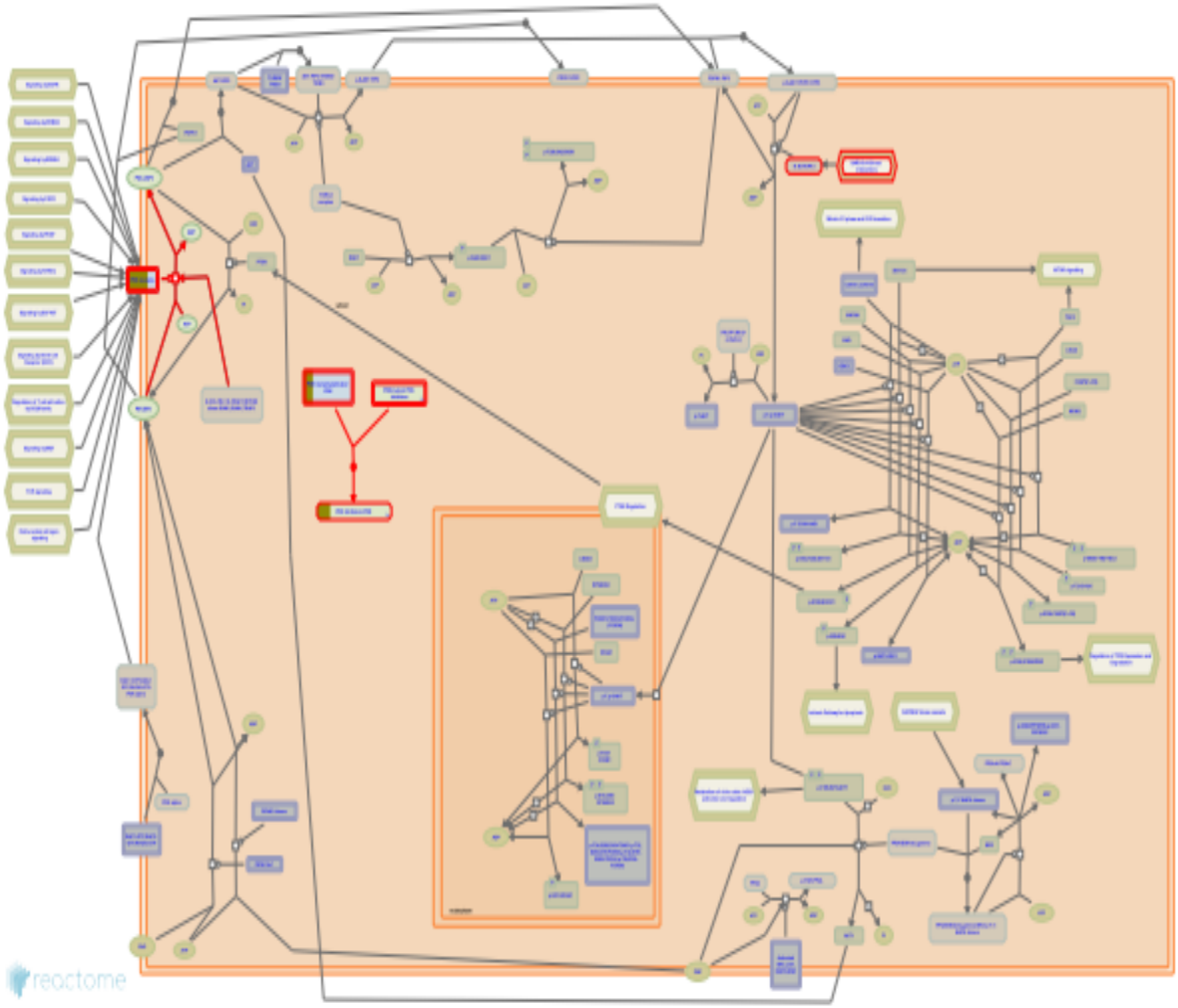
Sorting in select nodes Sorting in whole network

No.	Name	Degree	Betweenness	Closeness
1	9606.ENSP00000269305	4.0	0.0	1.0
2	9606.ENSP00000405330	4.0	0.0	1.0
3	9606.ENSP00000263967	4.0	0.0	1.0
4	9606.ENSP00000369497	4.0	0.0	1.0
5	9606.ENSP00000261769	4.0	0.0	1.0

6)Pathway Analysis-
REACTOME-
Pathways details-

For every pathway of the most significant pathways, we present its diagram, as well as a short summary, its bibliography and the list of inputs found in it.

1. Constitutive Signaling by Aberrant PI3K in Cancer (R-HSA-2219530)-

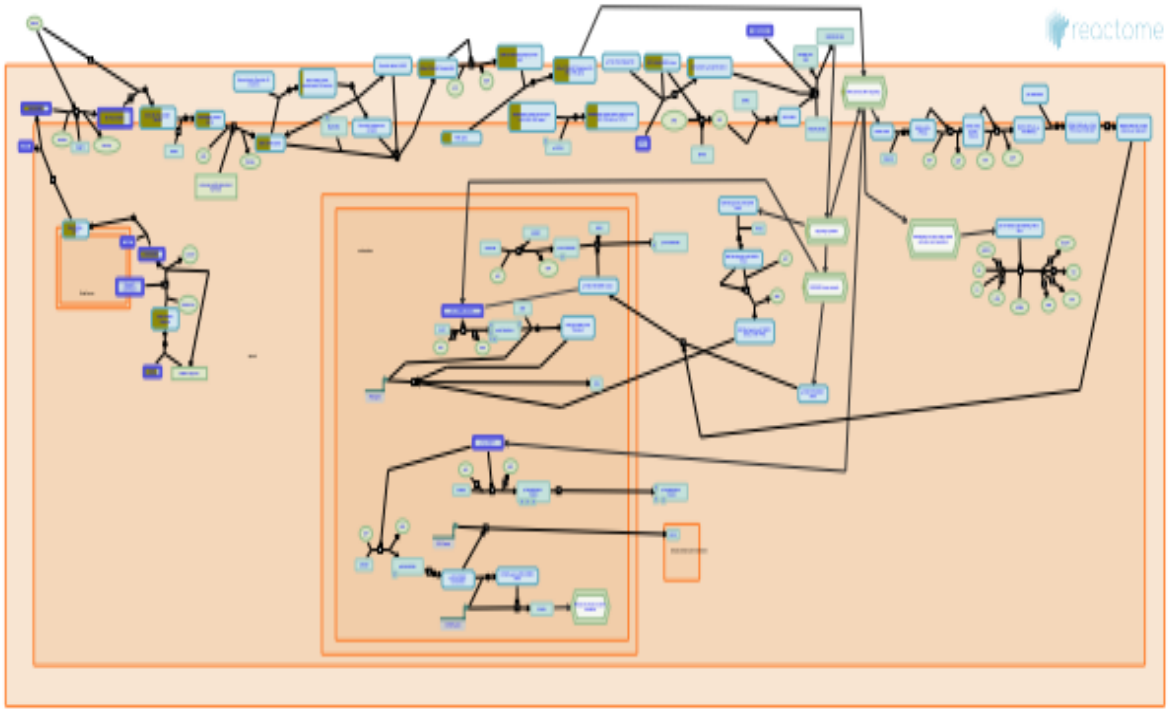


PI3K/AKT Pathway Activation in Cancer

In many cancers, the PI3K/AKT signaling pathway is persistently activated due to gain-of-function mutations in either of the two subunits of PI3K—PIK3CA, which codes for the catalytic subunit p110α, or PIK3R1, which encodes the regulatory subunit p85α. These genetic alterations enhance PI3K signaling through various mechanisms. For instance, mutations in the helical domain of PIK3CA or in the nSH2 and iSH2 domains of PIK3R1 disrupt the normal inhibitory regulation between the two subunits, though they still remain physically associated. Meanwhile, mutations in the catalytic domain of PIK3CA allow the enzyme to adopt an active conformation more readily.

As a result of these mutations, PI3K becomes constitutively active, generating PIP3 and triggering downstream activation of AKT without requiring external growth signals. This unregulated activation contributes significantly to tumor development and progression (as supported by studies such as Huang et al., 2007; Zhao et al., 2005; Miled et al., 2007; Horn et al., 2008; Sun et al., 2010; Jaiswal et al., 2009; Zhao & Vogt, 2010; Urick et al., 2011). (15,16.171.18,19)

2. Extra-nuclear estrogen signaling (R-HSA-9009391)



Non-Genomic Estrogen Signaling and Its Cellular Impacts

Beyond its traditional role in regulating gene expression through nuclear estrogen receptors, beta-estradiol (E2) also initiates rapid, non-genomic signaling events via receptors located at the plasma membrane. This membrane localization is driven by dynamic palmitoylation of estrogen receptors, a modification essential for initiating E2-mediated extra-nuclear signaling, as demonstrated in both cell-based and animal studies (Acconcia et al., 2004; Acconcia et al., 2005; Marino et al., 2006; Marino & Ascenzi, 2006).

The activation of these fast-acting signaling pathways also requires methylation of the estrogen receptor ESR1 by the enzyme PMRT1 (Pedram et al., 2007; Pedram et al., 2012; Le Romancer et al., 2008; Arnal, 2017; Le Romancer et al., 2011). These non-genomic responses occur within seconds to minutes following E2 exposure and are independent of the receptor's transcriptional activity.

These rapid signaling events include the activation of key cellular pathways such as the RAF/MAPK and PI3K/AKT cascades, which play major roles in cell survival, proliferation, apoptosis, and metastasis (Hammes et al., 2007; Handa et al., 2012; Lange et al., 2007; Losel et al., 2003; Arnal et al., 2017; Le Romancer et al., 2011). Moreover, estrogen receptor-mediated signaling interacts with other major signaling systems, including receptor tyrosine kinases, NF-κB, and GPCRs, by influencing protein post-translational modifications and second messenger pathways (Arnal et al., 2017; Schwartz et al., 2016; Boonyaratanakornkit, 2011; Biswas et al., 2005).

In the brain, E2's non-genomic actions influence various neural processes such as cognition, mood, stress response, and reproduction (Farach-Carson & Davis, 2003; Losel et al., 2003). In vascular endothelial cells, this mode of signaling contributes to vasodilation by activating the eNOS pathway (Levin, 2011).

Interestingly, these membrane-initiated signals can also feed back to regulate the stability of the estrogen receptor itself and intersect with nuclear signaling mechanisms (La Rosa et al., 2012). Recent findings have revealed that membrane-bound ESR1 interacts with endocytic machinery and translocates within the cell via interactions with transmembrane receptors like IGF1R and β1-integrin, highlighting a novel layer of

receptor trafficking and signaling within the cytoplasm (Sampayo et al., 2018). (20,21,22,23)

RESULT AND DISSCUSSION

- Genes linked to the lead and receptor molecules were examined in the presence investigation.
- The current study uses the Pubchem program to identify the grins of molecules. These smiles were integrated into the sophisticated program known as "swiss target prediction," which obtained uniport ids for both the genes and the receptors.
- The current study then discovered that more genes were obtained from the SEA tool and from the colchicine molecule utilizing a variety of tools, including Swiss target prediction, Malacards, Omim and Disgenet. Additionally, common genes were found using an AI tool.
- Venny 2.1.0 used to obtain common gene.
- Reactome software was then utilized to obtain illness pathways, and a string tool from Cytoscape was employed for centrality metrics in the current Network Pharmacology study.
- As a result, network pharmacology offers fresh perspectives on drug action analysis.

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