Network Pharmacology of Gymnemic Acid

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Abstract- Gymnemic acid, a group of triterpenoid saponins primarily extracted from Gymnema sylvestre, has attracted significant interest due to its potent antidiabetic properties. This study explores the pharmacological relevance of gymnemic acid in glycemic control, focusing on its molecular mechanisms, inhibition of intestinal glucose absorption, and stimulation of insulin secretion. The findings suggest gymnemic acid may offer a natural, effective therapeutic option for managing type 2 diabetes mellitus with minimal side effects.

Keywords: Gymnemic acid, Gymnema sylvestre, antidiabetic, glucose absorption, insulin secretion

INTRODUCTION OF NETWORK PHARMACOLOGY

Network Pharmacology (NP) is an emerging scientific discipline that seeks to understand how drugs interact with multiple biological targets within complex biological systems. Rather than focusing on a single target, NP explores the broader network of interactions among genes, proteins, pathways, and small molecules to determine potential intervention points for therapeutic agents.
Originally proposed by British pharmacologist Andrew L. Hopkins in a 2007 article in Nature Biotechnology, network pharmacology is rooted in the integration of pharmacology, systems biology, and bioinformatics. Its development has been fueled by the rapid growth of network databases and computational biology.

Core Techniques in Network Pharmacology:

- Biological Function Analysis – Understanding the biological roles of genes and proteins within networks.
- Network Construction and Visualization – Building and visually representing the interactions between different molecular entities.
- Prediction Modeling – Forecasting how potential drugs might interact with the network.
- Topological Analysis – Studying the structural attributes of networks to identify key regulatory nodes or hubs.

Insights Offered by NP:

- By analyzing relationships between nodes (genes, proteins, etc.) in a biological network, NP can uncover new mechanisms of drug action.
- It also aids in identifying potential adverse drug reactions and novel therapeutic targets.

TYPES OF NETWORK PHARMACOLOGY

1. Compound-Target Network Analysis:
This approach investigates how one or more compounds interact with multiple biological targets. It is particularly useful for understanding the poly pharmacological properties of drugs, especially in complex diseases that involve multiple genes and pathways. By mapping compounds to their potential targets, researchers can explore possible mechanisms of action and optimize drug design accordingly.

1. Target-Disease Network Analysis:
This approach investigates how medications interact with multiple disease-related targets. It also includes network-based disease gene prediction, which identifies potential disease genes by analyzing their connections within biological networks.
2. Drug Target Prediction:
This method leverages network analysis to anticipate which biological targets (such as proteins or genes) a drug is most likely to affect.
3. Drug Function Prediction:
Through the study of network patterns and molecular interactions, this approach forecasts the likely functions or therapeutic effects of specific drugs.
4. Network Construction for Chinese Herbal Medicine:
This involves creating detailed interaction networks for herbal compounds and their biological targets, helping to decode the multi-component, multi-target mechanisms of traditional Chinese medicine.

Core Concepts of Network Pharmacology
Network pharmacology is a modern interdisciplinary field that merges pharmacology,

systems biology, and computational modeling to explore the complex web of interactions between drugs and biological systems. Unlike traditional pharmacology, which typically investigates the effects of a single drug on a single target, this approach considers the entire system, mapping how multiple compounds affect a wide range of targets and biological processes.

MOLECULAR INTRODUCTION

Molecule Name: Gymnemic Acid

Source Plant: Derived from the leaves of Gymnema sylvestre

Commercial Names: Commonly found as Gymnema extract, Gurmar, or "Sugar Destroyer" in traditional medicine

Oral Bioavailability: Generally low when taken orally; however, bioavailability may be improved using advanced formulation technologies

Plasma Protein Binding: Exact values are not well-defined, but moderate binding is expected due to its saponin-based structure

Metabolic Pathway: Presumed to undergo hepatic metabolism; the specific involvement of cytochrome P450 enzymes is not well established

Biological Half-life: The elimination half-life has not been precisely quantified; it may vary depending on dosage and formulation type

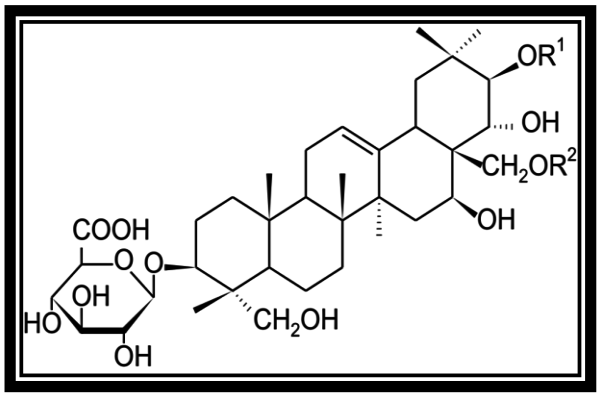
Route of Elimination: Primarily excreted through feces, reflecting poor absorption and limited systemic distribution

Chemical IUPAC Name: (2S,4S,5R)-2-[(2R,3S,4R,5R,6S)-3,4-dihydroxy-2,5,6-trimethyloxan-3-yl] oxy-5-hydroxy-4-methyltetrahydro-2H-pyran-3-carboxylic acid (represents one of several gymnemic acid variants)

MOA OF GYMNEMIC ACID-

Gymnemic acid works primarily by interacting with the taste receptors and glucose absorption mechanisms in the body. It temporarily suppresses the ability to taste sweetness by blocking sugar receptors on the tongue, leading to reduced sugar cravings. In the intestine, gymnemic acid competes with glucose molecules for absorption by binding to intestinal receptors, thereby limiting the entry of glucose into the bloodstream. This helps in moderating postprandial blood sugar levels.

Additionally, gymnemic acid may stimulate insulin secretion and help in the regeneration of pancreatic beta cells, contributing to improved glycemic control. Its action also includes inhibition of enzymes involved in carbohydrate digestion, such as α-amylase and α-glucosidase, which slows the breakdown of complex sugars.

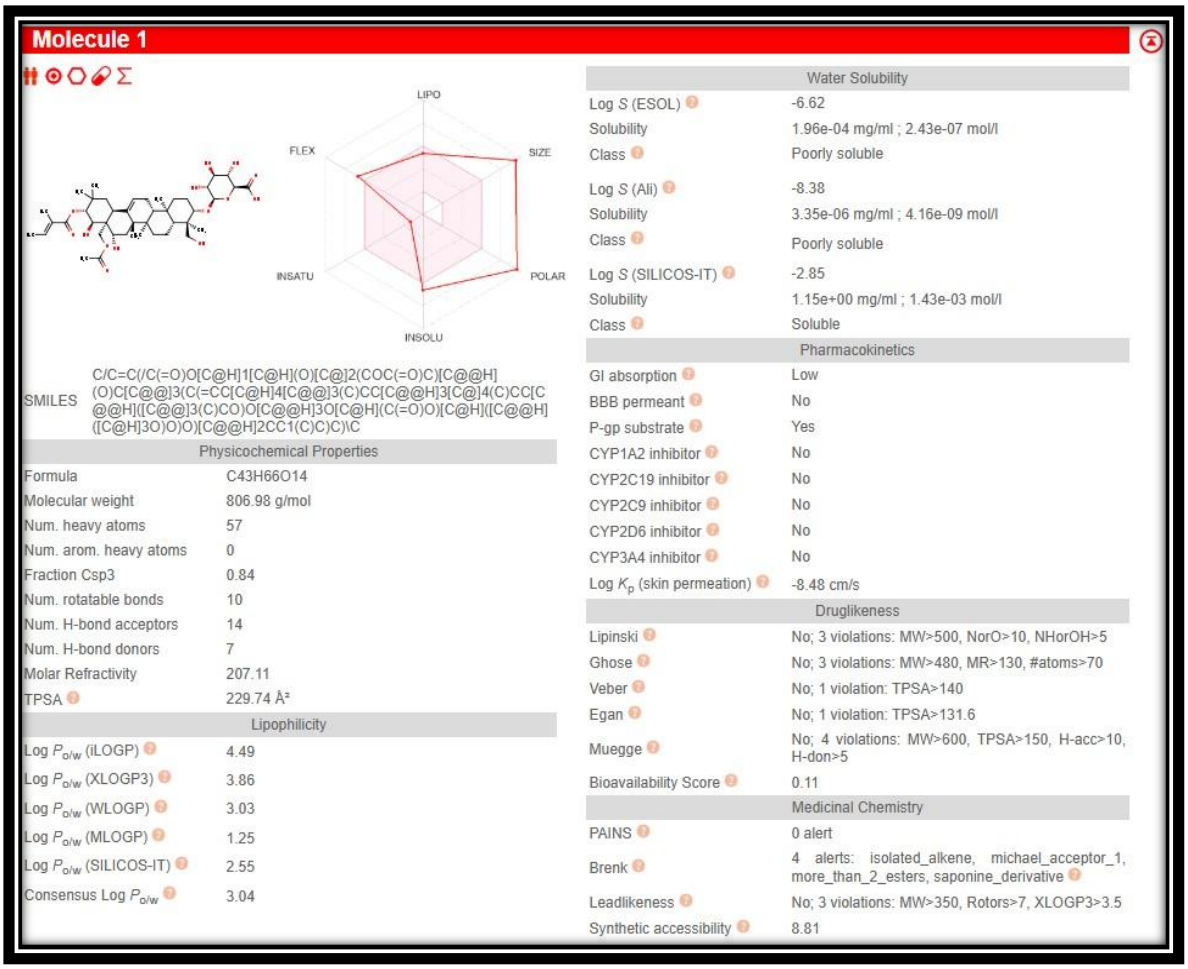


Use of Gymnemic Acid-

1. Blood Glucose Control
2. Decreasing Cravings for Sweets
3. Assistance in Weight Loss
4. Antioxidant and Anti-inflammatory Benefits
5. Promoting Digestive Wellness
6. Managing Cholesterol Levels

MATERIAL AND METHOD-

SMILIES OF Gymnemic Acid
PUBCHEM
C/C=C(\C)/C(=O)O[C@H]1[C@@H]([C@@]2([C@H](C[C@@]3(C(=CC[C@H]4[C@]3(CC[C@@H]5[C@@]4(CC[C@@H]([C@@]5(C)CO)O[C@H]6[C@@H]([C@H]([C@@H]([C@H](O6)C(=O)O)O)O)O)C)C)[C@@H]2CC1(C)C)C)O)COC(=O)C)O



Molecule 1

SMILES: C/C=C(/C(=O)O[C@H]1[C@H](O)[C@]2(COC(=O)C)[C@@H](O)C[C@@]3(C(=CC[C@H]4[C@@]3(C)CC[C@@H]3[C@]4(C)CC[C@@H]([C@@]3(C)CO)O[C@@H]3O[C@H](C(=O)O)[C@H]([C@@H]([C@H]3O)O)O)[C@@H]2CC1(C)C)C)\C

Physicochemical Properties	
Formula	C43H66O14
Molecular weight	806.98 g/mol
Num. heavy atoms	57
Num. arom. heavy atoms	0
Fraction Csp3	0.84
Num. rotatable bonds	10
Num. H-bond acceptors	14
Num. H-bond donors	7
Molar Refractivity	207.11
TPSA	229.74 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.49
Log $P_{o/w}$ (XLOGP3)	3.86
Log $P_{o/w}$ (WLOGP)	3.03
Log $P_{o/w}$ (MLOGP)	1.25
Log $P_{o/w}$ (SILICOS-IT)	2.55
Consensus Log $P_{o/w}$	3.04

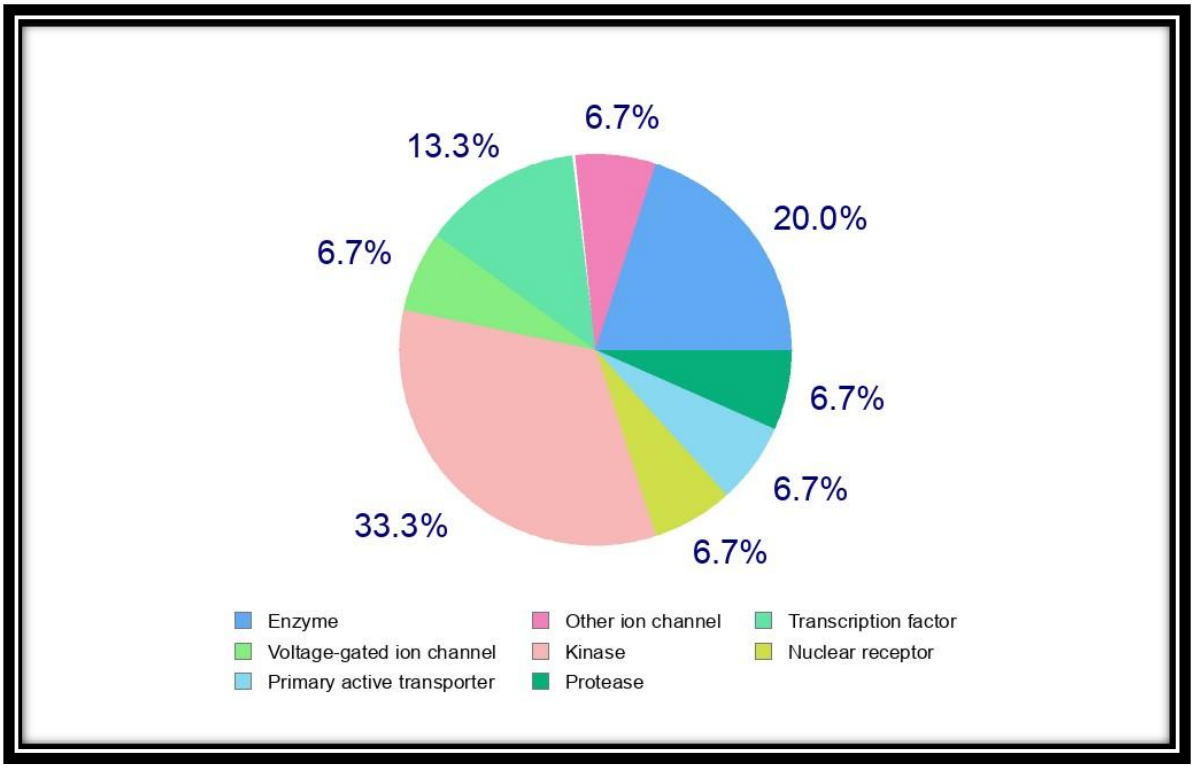
Water Solubility	
Log *S* (ESOL)	-6.62
Solubility	1.96e-04 mg/ml ; 2.43e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-8.38
Solubility	3.35e-06 mg/ml ; 4.16e-09 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-2.85
Solubility	1.15e+00 mg/ml ; 1.43e-03 mol/l
Class	Soluble

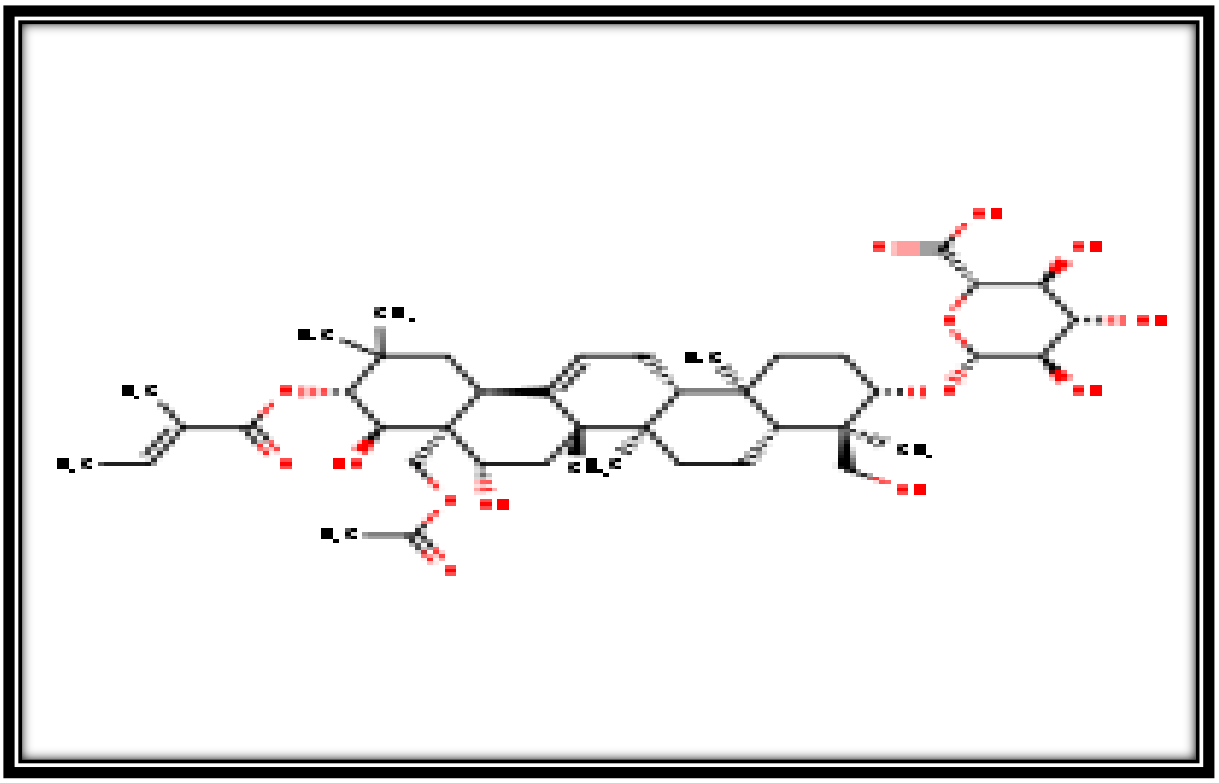
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.48 cm/s

Druglikeness	
Lipinski	No; 3 violations: MW>500, NorO>10, NHorOH>5
Ghose	No; 3 violations: MW>480, MR>130, #atoms>70
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 4 violations: MW>600, TPSA>150, H-acc>10, H-don>5
Bioavailability Score	0.11

Medicinal Chemistry	
PAINS	0 alert
Brenk	4 alerts: isolated_alkene, michael_acceptor_1, more_than_2_esters, saponine_derivative
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	8.81

2) Selection of Target Identification -
SWISS TARGET





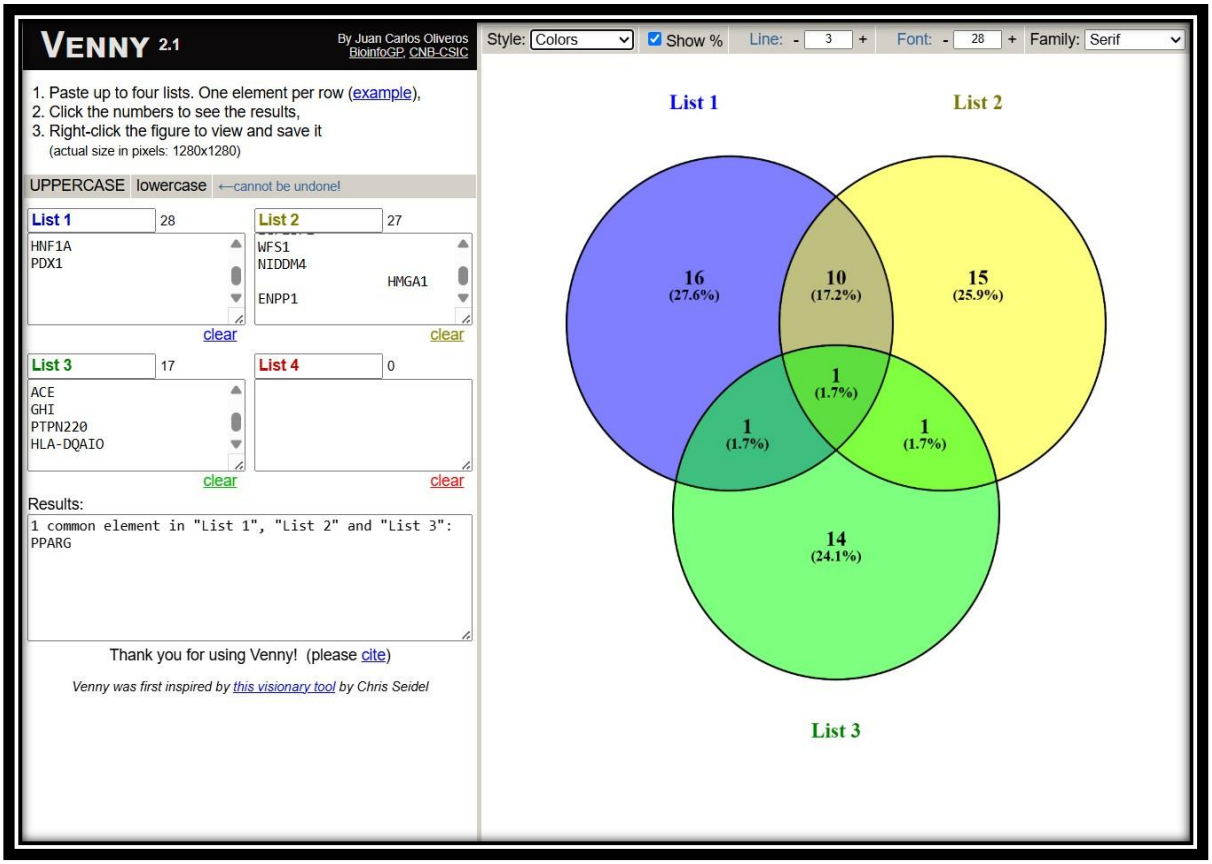
3) Disease Gene –

OMIM	MALACARD-	DISGENET-	
NEUROD1	GPD2	MIR17	INS
IRS1	NEUROD1	MIR145	DPP4
PPARG	IRS1	MIR375	GLP1R
PPARG	PPARG	MIR140	ADIPOQ
SLC2A2	PPARG	MIR132	PPARG
IGF2BP2	SLC2A2	MIR30E	TCF7L2
WFS1	IGF2BP2	MIR197	ACE
NIDDM4	WFS1	MIR99A	IAPP
HMGA1	NIDDM4	GCK	LEP
ENPP1	HMGA1	RFX6	TNF
IL6 GCK	ENPP1	SPINK1	INS
PPP1R3A	IL6 GCK	MEN1	CTLA4
PAX4	PPP1R3A	CELA2A	IGFI
SLC30A8	PAX4	MIR155	GAD2
TCF7L2	SLC30A8	INS	PTPRN
ABCC8	TCF7L2	KCNJ11	TNF
MAPKSIP1	ABCC8	WFS1	ACE
MTNRIB	MAPKSIP1	HNF1A	GHI
HNF1A	MTNRIB	GPD2	PTPN220
PDX1	HNF1A	NEUROD1	HLA-DQAIO
IRS2	PDX1	IRS1	
LIPC	KCNJ11	PPARG	
HNF1B	WFS1	SLC2A2	
RETN	HNF1A	IGF2BP2	
RETN	GCK	WFS1	
AKT2	RFX6	NIDDM4	
HNF4A	SPINK1	HMGA1	
PTPN1	MEN1	ENPP1	
GPD2	CELA2A		
NEUROD1	MIR155		
IRS1	MIR17		
PPARG			
PPARG			

4) Selection Of Common Gene

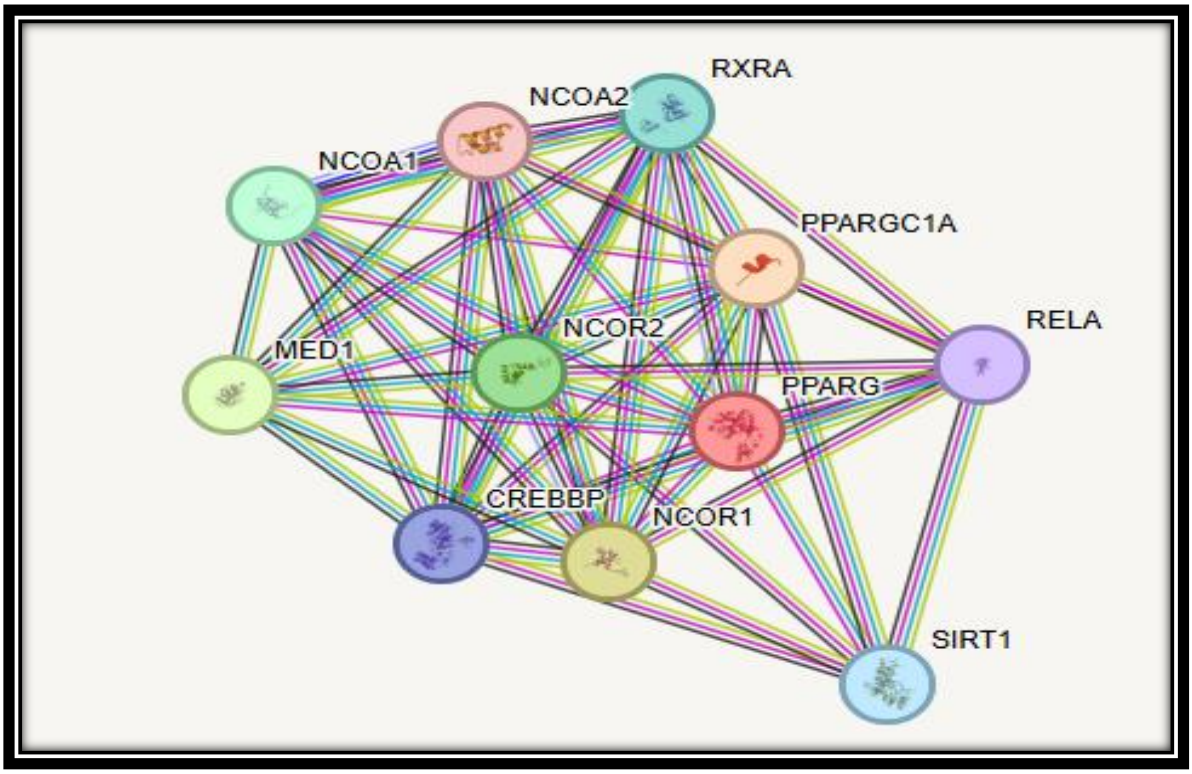
VENNY-

- PPARG



5) PPI Intraction and ranking-

STRING DATA-



CYTOSCAPE- Centrality measure

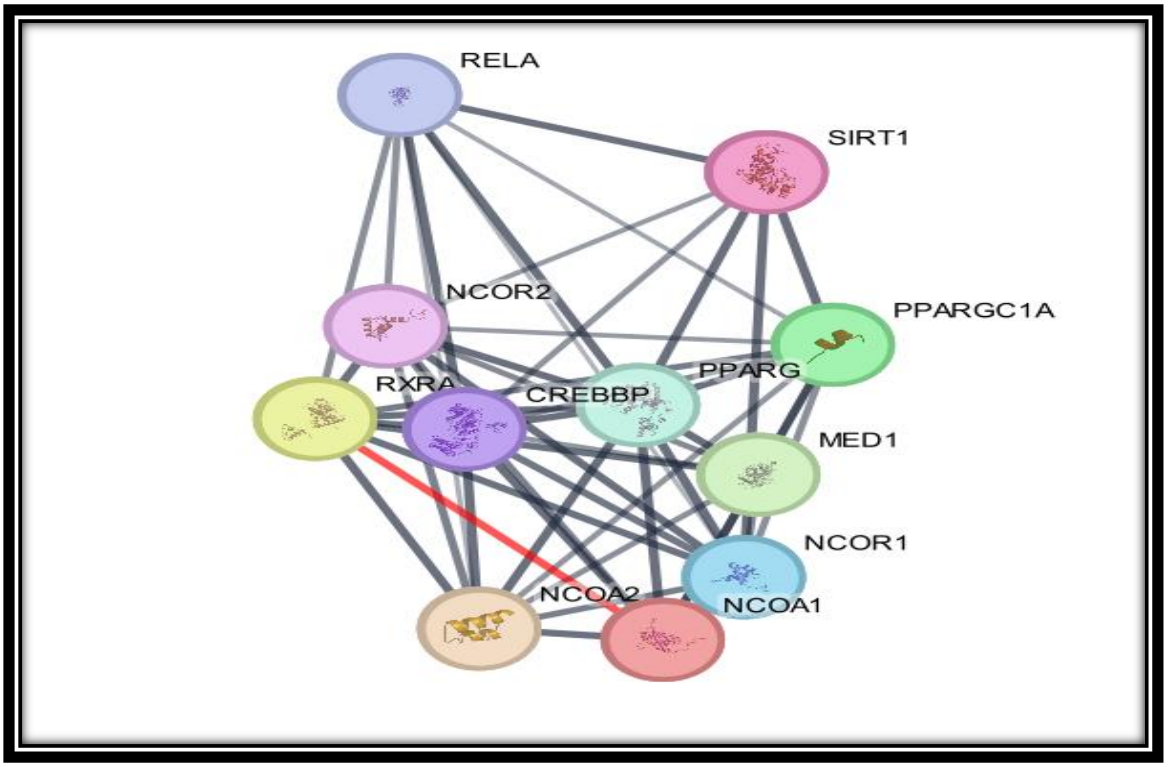
Results Panel

Result 1

Result List(11 in total)

Sorting in select nodes Sorting in whole network

No.	Name	Degree	Betweenness	Closeness
1	9606.ENSP00000264867	10.0	2.038095238095238	1.0
2	9606.ENSP00000287820	10.0	2.038095238095238	1.0
3	9606.ENSP00000268712	10.0	2.038095238095238	1.0
4	9606.ENSP00000262367	10.0	2.038095238095238	1.0
5	9606.ENSP00000384018	10.0	2.038095238095238	1.0
6	9606.ENSP00000399968	9.0	0.5714285714285714	0.9090909090909091
7	9606.ENSP00000419692	9.0	0.5714285714285714	0.9090909090909091
8	9606.ENSP00000385216	8.0	0.0	0.8333333333333334
9	9606.ENSP00000300651	8.0	0.0	0.8333333333333334
10	9606.ENSP00000384273	8.0	0.6666666666666666	0.8333333333333334
11	9606.ENSP00000212015	6.0	0.0	0.7142857142857143

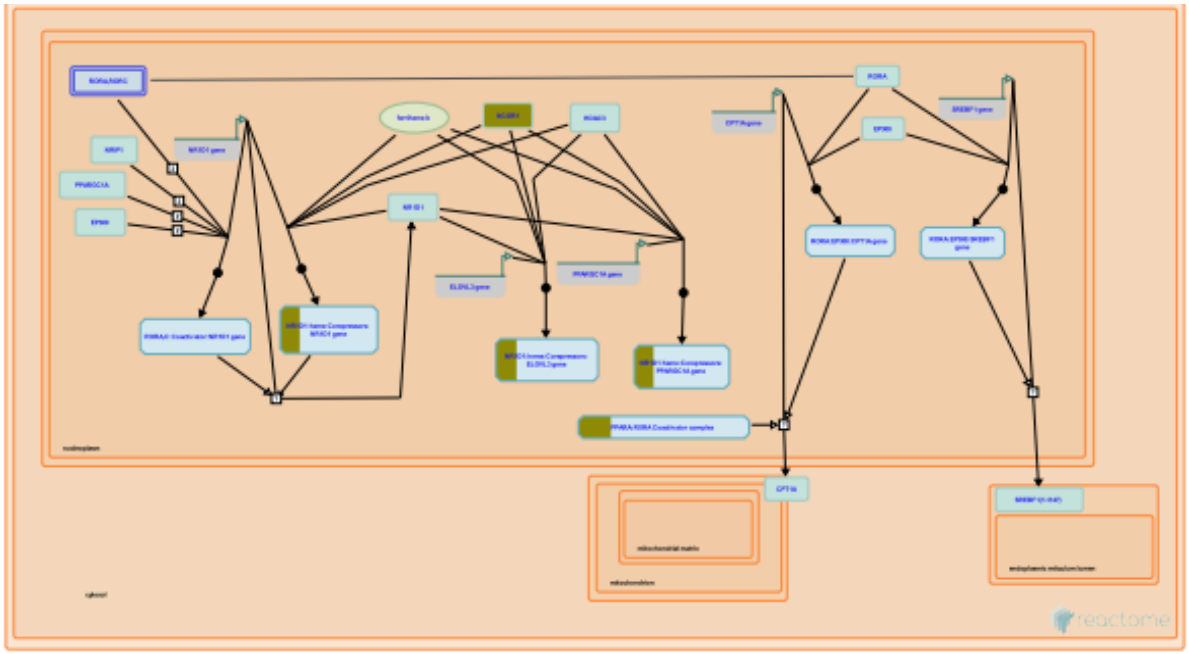


7) PATHWAY ANALYSIS REPORT-

REACTOME-

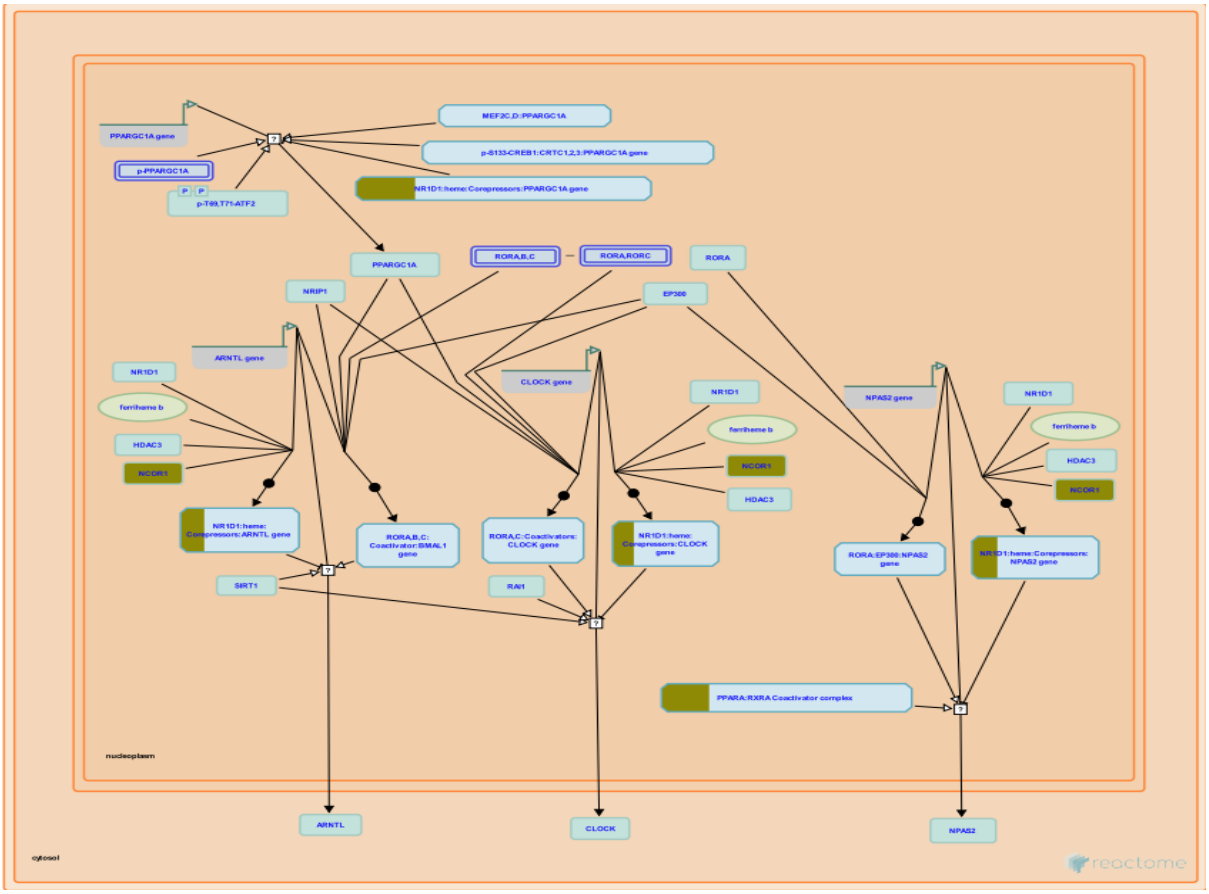
PATHWAT DETAILS-

1. RORA, B, C and NR1D1 (REV-ERBA) regulate gene expression (R-HSA-9933387)-



The retinoid-related orphan receptors (RORA, RORB, and RORC) and the heme-binding nuclear receptor NR1D1 (also known as REV-ERBα) both attach to ROR response elements (ROREs) within DNA sequences. Despite targeting the same DNA regions, these two types of receptors function oppositely. RORs enhance gene transcription by attracting coactivators like EP300 (p300) and PPARGC1A. In contrast, NR1D1 suppresses transcription by recruiting corepressors such as NCOR1 and histone deacetylase HDAC3, leading to gene silencing. (26,27,28)

2. Expression of BMAL (ARNTL), CLOCK, and NPAS2 (R-HSA-9931509)-



BMAL1 (also known as ARNTL), CLOCK, and NPAS2 (a functional substitute for CLOCK) serve as major drivers of daily circadian gene expression patterns (see Cox and Takahashi, 2019 for review). The activity of these genes is upregulated by retinoic acid receptor-related orphan receptors—RORA, RORB, and RORC—and downregulated by the nuclear receptor NR1D1 (REV-ERBA). All of these transcription factors compete for binding to ROR response elements (RRE or RORE) located in the promoters of BMAL1 and CLOCK genes (evidence based on mouse studies: Ueda et al., 2002; Guillaumond et al., 2005; Sato et al., 2004; Akashi and Takumi, 2005; Takeda et al., 2012; Lau et al., 2004).

The ROR receptors interact with oxysterols (Wang et al., 2010), while NR1D1 binds to heme (Yin et al., 2007; Raghuram et al., 2007), suggesting a link between circadian regulation and metabolic signals. To enhance gene transcription, RORs recruit transcriptional coactivators like EP300 (p300), PPARGC1A (PGC1A), and NRIP1 (evidence from Lau et al., 2004; Poliandri et al., 2011). Conversely, NR1D1 bound to heme attracts repressor complexes including NCOR1 and the histone deacetylase HDAC3 to suppress transcription (Wu et al., 2009).

Importantly, BMAL1 and CLOCK not only regulate downstream targets but also modulate the expression of RORA, RORC, and NR1D1, forming a feedback loop essential for maintaining circadian rhythm stability. (29,30,31,32,33,34,36,36)

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 Ajmalicine molecule utilizing a variety of tools, including Swiss target prediction, Malacards, Omim and Disgenet. Additionally, common genes were found using an Al 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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