Network pharmacology of 10-gingerol

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***Abstract*—The present study explores the therapeutic potential of 10-gingerol, a key bioactive compound derived from Zingiber officinale, using an integrated network pharmacology and molecular modeling approach. 10-Gingerol is known for its diverse pharmacological properties, including anti-inflammatory, antioxidant, anticancer, and antimicrobial activities. To elucidate its multi-target mechanisms, potential gene and receptor interactions were identified using Swiss Target Prediction and cross-validated with databases such as SEA, MalaCards, OMIM, and DisGeNET. Common gene targets were refined using AI-assisted tools and Venny 2.1.0, while pathway enrichment analysis was performed using the Reactome Pathway Database. Cytoscape and STRING were employed to construct and analyze protein-protein interaction networks, emphasizing central nodes based on topological features. Molecular modeling techniques provided insights into binding affinities and structural interactions at the atomic level. The study reveals that 10-gingerol modulates key signaling pathways, particularly those involved in inflammation, cancer, and metabolic disorders. These findings demonstrate the power of combining computational approaches to deepen mechanistic understanding and advance the development of natural product-based therapeutics.**

***Index Terms*—Network Pharmacology, Gene,10-Gingerol**

I. INTRODUCTION OF NETWORK PHARMACOLOGY

In order to investigate how medications, targets, and illnesses interact within a biological network, network pharmacology combines pharmacology, systems biology, and bioinformatics.

It seeks to comprehend drug mechanisms of action, anticipate the safety and efficacy of novel drug candidates, and pinpoint the intricate interactions that exist between medications and their targets.

On the other hand, molecular modeling is a computational method that simulates and forecasts the structure and behavior of molecules at the molecular level using physical and chemical concepts.

It can be used to anticipate a medication's binding affinity to a target protein, investigate how pharmaceuticals interact with their targets, and create novel therapeutic compounds that are more potent and selective.

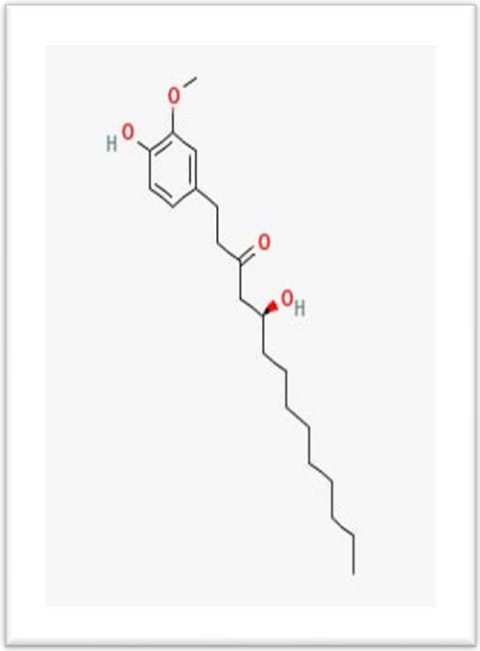
Because they assist identify possible drug targets, shed light on how medications work, and make it easier to create new therapeutic agents, network pharmacology and molecular modeling are both effective techniques in drug discovery and development. Researchers can find new drug candidates, streamline drug development procedures, and increase the effectiveness and safety of medications for a range of illnesses by combining these two strategies.

Molecular Introduction

• 10. Gingerol= The main bioactive ingredient in ginger (Zingiber officinale) is 10-gingerol, which has anti-inflammatory, antioxidant, and anti-cancer properties. It is responsible for ginger's unique spicy taste and has been researched for potential therapeutic benefits such as nausea reduction and pain treatment. Recent studies have shown that 10-gingerol can both boost the immune system and inhibit the growth of tumors. It is a common component of nutritional supplements and natural medicine due to its pharmacological qualities.

• The essential details =10-Gingerol The well-liked herbal and spice remedy the main source of the bioactive compound gingerol is ginger (Zingiber officinale).

• Structure of 10-gingerol:



The following are some essential details about 10-gingerol:

• chemical formula is=C17H26O4 .
• The molecular weight is 294.39 g/mol.
• The IUPAC name is = (3S).((2S)) 1-hydroxy-3-phenylbutan-2-ylThe compound 4-hydroxy-3-methoxyphenylMethane

• source = 10-gingerol, which is mostly obtained from the rhizomes of the plant, is one of the main phenolic compounds in ginger, along with 6-gingerol and 8-gingerol.

• characteristics of biology
1. Anti-inflammatory Effects: Studies have shown that 10-gingerol has anti-inflammatory properties by inhibiting pro-inflammatory cytokines and enzymes.
2. Antioxidant Activity: Protecting cells from oxidative damage is made easier by its antioxidant qualities.
3. Anticancer Properties: Research indicates that 10-gingerol may stop tumors from growing and induce apoptosis in cancer cells.

SWISS ADME

4. Antimicrobial Activity: It has demonstrated antibacterial and antifungal qualities against a variety of illnesses.
5. Gastroprotective Effects: Studies suggest that it may protect the gastrointestinal tract and reduce the symptoms of gastrointestinal disorders.

• Mechanism of Action:
10-Among other things, gingerol acts by altering signaling pathways connected to inflammation and the emergence of cancer. It may affect the NF-κB pathway, among other things.

Safety and Toxicity: Although concentrated supplements or high dosages may upset some people's stomachs, they are usually safe when taken in food amounts.

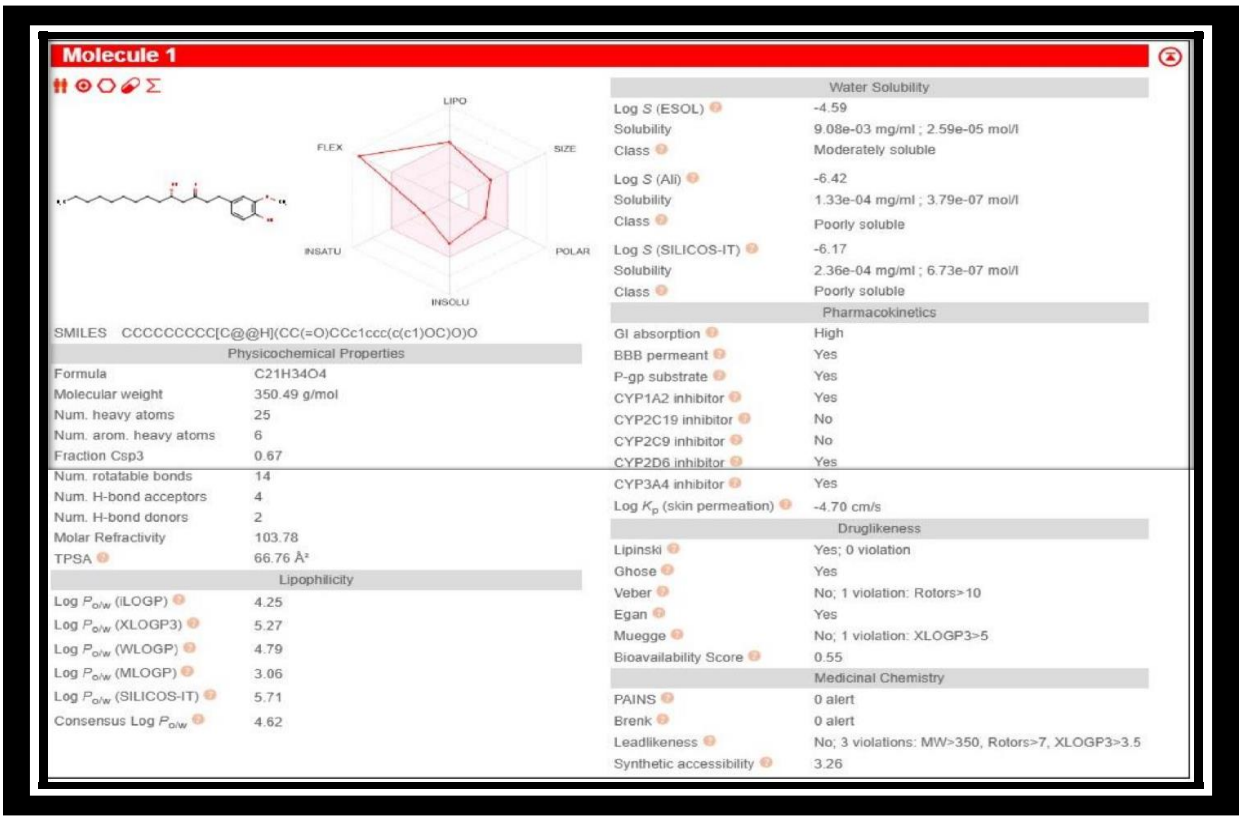
Utilizing 10-gingerol
1. Action Against Cancer: -Induction of apoptosis and suppression of cell division: Chemotherapy in combination
2. Anti-inflammatory and Antioxidant Properties:
• Antioxidant Effects: 10-gingerol exhibits antioxidant activity, presumably by increasing the levels of the antioxidant enzymes CAT and GPx.
• Anti-Inflammatory Effects: By boosting adiponectin and reducing resistin and TNFα levels, it can diminish LPS-induced inflammation in adipocytes.
• 3. Additional Possible.
Uses: Antimicrobial Action
: Against obesity

[3]

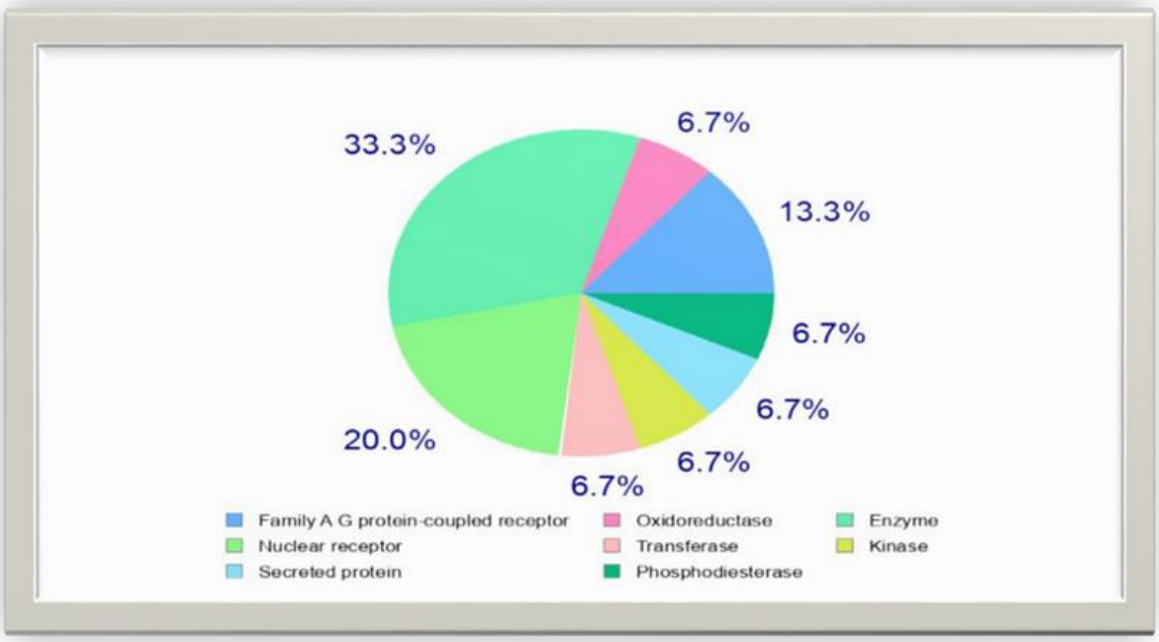
II. MATERIALS AND METHOD

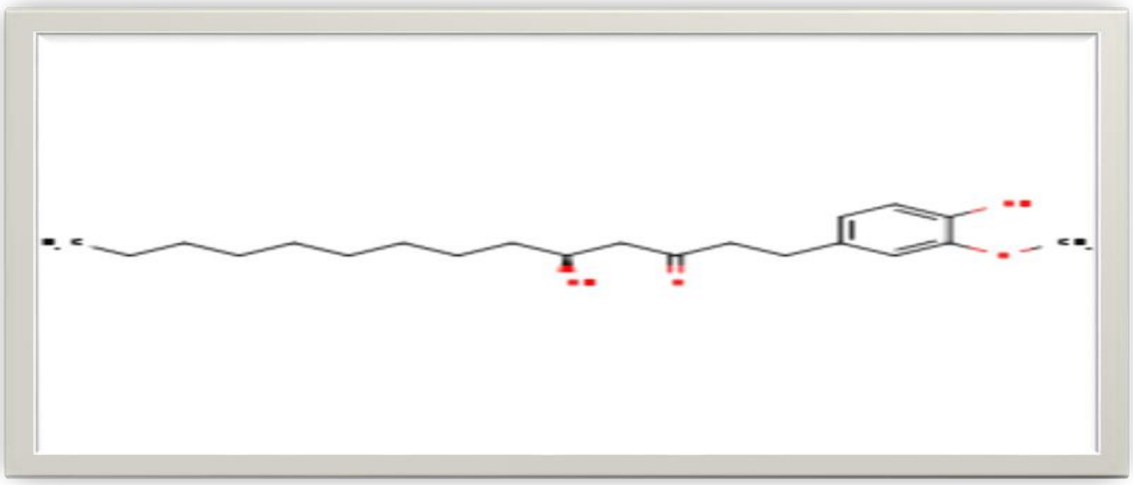
1) Selection of Phytochemical-

SMILIES OF 10-GINGEROL: -
CCCCCCCCC[C@@H](CC(=O)CCC1=CC(=C(C=C1)O)OC)O



2) Selection of Target Identification
SWISS TARGET





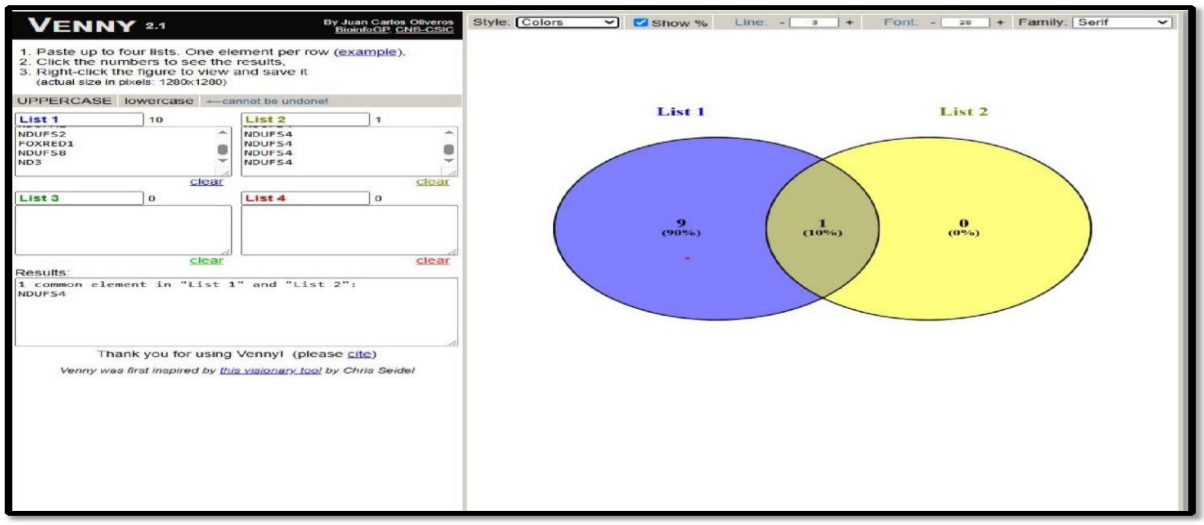
3) Disease Gene –
DISGENET

Gene	Gene Full Name	N Diseases$_g$	N Variants$_g$	Score$_{gda}$	N PMIDs	N Chemicals	N PMIDs Chem
NDUFS4	NADH:ubiquinone oxidoreductas...	160	38	1	26	0	0
NDUFS1	NADH:ubiquinone oxidoreductas...	147	105	0.9	15	2	1
NDUFV1	NADH:ubiquinone oxidoreductas...	110	83	0.75	28	3	2
NDUFS6	NADH:ubiquinone oxidoreductas...	80	29	0.75	7	0	0
NUBPL	NUBP iron-sulfur cluster assembl...	102	104	0.7	13	0	0
NDUFA1	NADH:ubiquinone oxidoreductas...	105	12	0.7	0	0	0
NDUFS2	NADH:ubiquinone oxidoreductas...	141	59	0.65	13	2	1
FOXRED1	FAD dependent oxidoreductase ...	97	70	0.65	11	0	0
NDUFS8	NADH:ubiquinone oxidoreductas...	94	37	0.65	9	2	1
MT-ND5	NADH dehydrogenase subunit 5	160	314	0.65	7	0	0

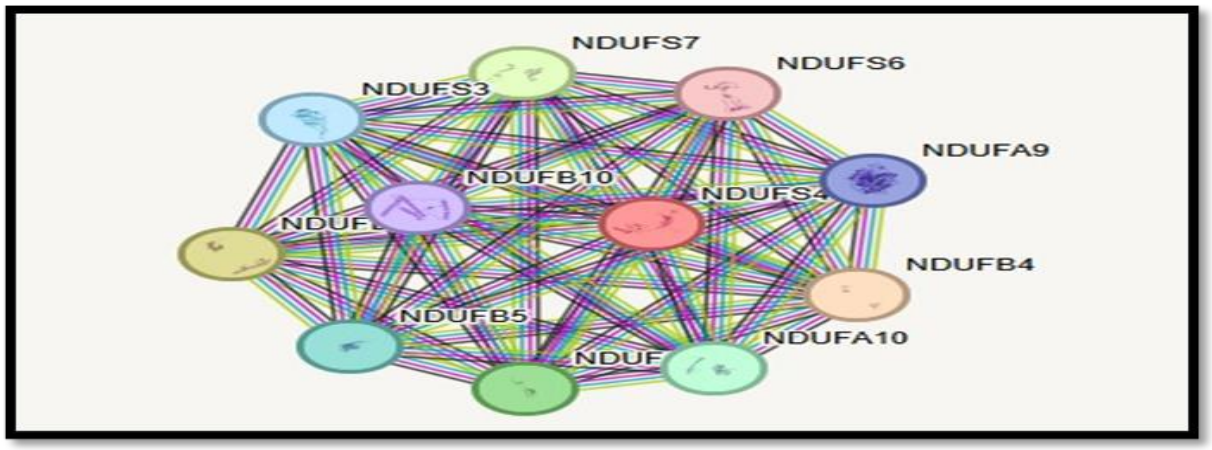
Gene	Score$_{gda}$	Association Type	Sentence	PMID	Reference Year
NDUFS4	1	Causalor Or Contrib...	Ndufs4 knockout mice with isolated complex I deficiency engage a f...	39395749	2024
NDUFS4	1	Causalor Or Contrib...	The NDUFS4 knockout (KO) mouse phenotype resembles the human ...	37883842	2023
NDUFS4	1	Genetic Variation	Mutations in the nuclear DNA-encoded NDUFS4 gene encoding the ...	34849584	2022
NDUFS4	1	Causal Mutation	Mutations in the nuclear DNA-encoded NDUFS4 gene encoding the ...	34849584	2022
NDUFS4	1	Causal Mutation	Uniparental isodisomy as a cause of mitochondrial complex I respira...	33093004	2020
NDUFS4	1	Genetic Variation	Disease-causing mutations in subunits of OXPHOS complex I affect c...	31292494	2019
NDUFS4	1	Genetic Variation	Exploring mTOR inhibition as treatment for mitochondrial disease.	31386302	2019
NDUFS4	1	Causalor Or Contrib...	Mitochondrial complex I deficiency leads to the retardation of early e...	28533980	2017
NDUFS4	1	Causalor Or Contrib...	Here we tested whether disruption of S6K1 can recapitulate the benef...	28919908	2017
NDUFS4	1	Genetic Variation	Mutations in the Complex I gene NDUFS4 lead to Leigh syndrome, whi...	26608563	2016

4) Selection Of Common Gene –

VENNY
NDUFS4



5) PPI intraction and ranking-
STRING DATA-



Cytoscape – Centrality Measure

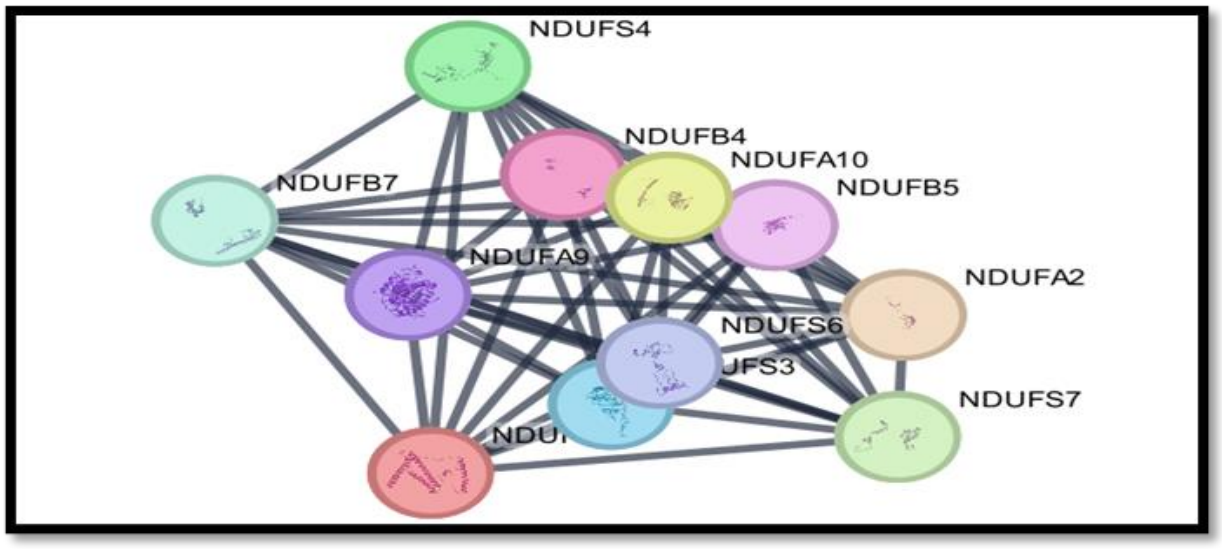
Results Panel

Result 1

Result List(11 in total)

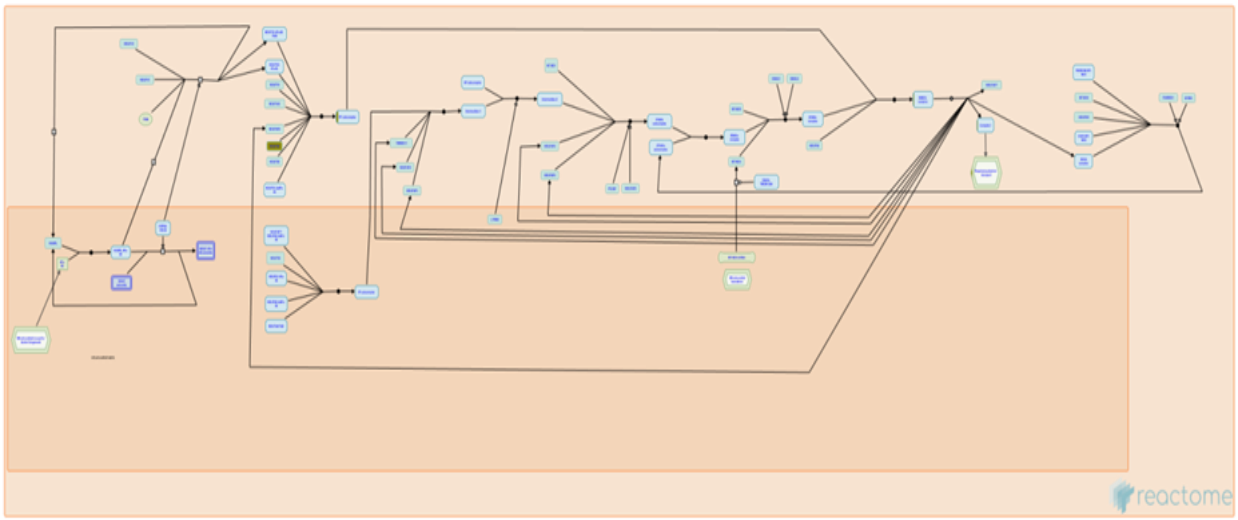
Sorting in select nodes Sorting in whole network

No.	Name	Degree	Betweenness	Closeness
1	9606.ENSP00000268668	10.0	0.0	1.0
2	9606.ENSP00000252102	10.0	0.0	1.0
3	9606.ENSP00000252711	10.0	0.0	1.0
4	9606.ENSP00000233627	10.0	0.0	1.0
5	9606.ENSP00000296684	10.0	0.0	1.0
6	9606.ENSP00000215565	10.0	0.0	1.0
7	9606.ENSP00000263774	10.0	0.0	1.0
8	9606.ENSP00000274137	10.0	0.0	1.0
9	9606.ENSP00000266544	10.0	0.0	1.0
10	9606.ENSP00000259037	10.0	0.0	1.0
11	9606.ENSP00000184266	10.0	0.0	1.0



6) Pathway Analysis-

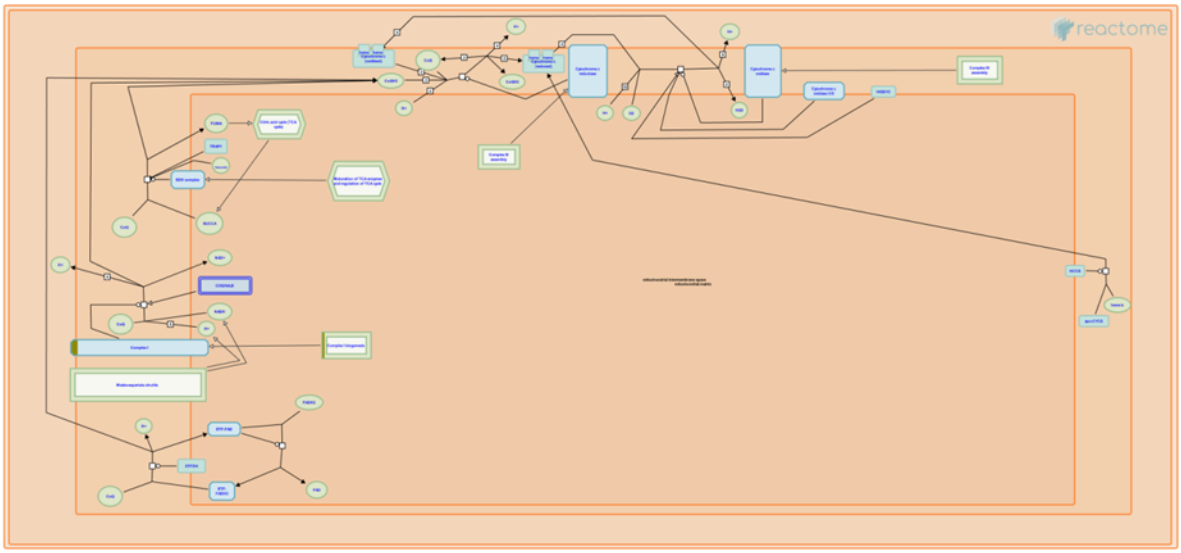
1. Complex I biogenesis (R-HSA-6799198)



Complex I (NADH:ubiquinone oxidoreductase or NADH dehydrogenase) utilises NADH formed from glycolysis and the TCA cycle to pump protons out of the mitochondrial matrix. It is the largest enzyme complex in the electron transport chain, containing 11 core and 34 accessory subunits. Seven subunits (ND1-6, ND4L) are encoded by mitochondrial DNA, the remainder are encoded in the nucleus. The enzyme has a FMN prosthetic group and 8 Iron-Sulfur (Fe-S) clusters. The subunits are assembled together in a coordinated manner via preassembled subcomplexes to form the mature holoenzyme. At least 24 so-called "assembly factor" proteins, acting intrinsically or transiently, are required for constructing complex I although their exact roles in the biogenesis are not fully understood (Fernandez-Vizarra et al. 2009, Mckenzie & Ryan 2010, Mimaki et al. 2012, Andrews et al. 2013 ; reviewed by Laube et al., 2024).([11],[12] .[13] .[14]

NDUFS4 O43181

2. Respiratory electron transport (R-HSA-611105)



Mitochondria are often described as the "powerhouse" of a cell as it is here that energy is largely released from the oxidation of food. Reducing equivalents generated from beta-oxidation of fatty acids and from the Krebs cycle enter the electron transport chain (also called the respiratory chain). During a series of redox reactions, electrons travel down the chain releasing their energy in controlled steps. These reactions drive the active transport of protons from the mitochondrial matrix , through the inner membrane to the intermembrane space. The respiratory chain consists of five main types of carrier; flavins, iron-sulfur centres, quinones, cytochromes (heme proteins) and copper. The two main reducing equivalents entering the respiratory chain are NADH and FADH2. NADH is linked through the NADH-specific dehydrogenase whereas FADH2 is reoxidised within succinate dehydrogenase and a ubiquinone reductase of the fatty acid oxidation pathway. Oxygen is the final acceptor of electrons and with protons, is converted to form water, the end product of aerobic cellular respiration. A proton electrochemical gradient (often called protonmotive force) is established across the inner membrane, with positive charge in the intermembrane space relative to the matrix. Protons driven by the proton-motive force, can enter ATP synthase thus returning to the mitochondrial matrix. ATP synthases use this exergonic flow to form ATP in the matrix, a process called chemiosmotic coupling. A by-product of this process is heat generation.

An antiport, ATP-ADP translocase, preferentially exports ATP from the matrix thereby maintaining a high ADP:ATP ratio in the matrix. The tight coupling of electron flow to ATP synthesis means oxygen consumption is dependent on ADP availability (termed respiratory control). High ADP (low ATP) increases electron flow thereby increasing oxygen consumption and low ADP (high ATP) decreases electron flow and thereby decreases oxygen consumption. There are many inhibitors of mitochondrial ATP synthesis. Most act by either blocking the flow of electrons (eg cyanide, carbon monoxide, rotenone) or uncoupling electron flow from ATP synthesis (eg dinitrophenol). Thermogenin is a natural protein found in brown fat. Newborn babies have a large amount of brown fat and the heat generated by thermogenin is an alternative to ATP synthesis (and thus electron flow only produces heat) and allows the maintenance of body temperature in newborns.

The electron transport chain is located in the inner mitochondrial membrane and comprises some 80 proteins organized in four enzymatic complexes (I-IV). Complex V generates ATP but has no electron transfer activity. In addition to these 5 complexes, there are also two electron shuttle molecules; Coenzyme Q (also known as ubiquinone, CoQ) and Cytochrome c (Cytc). These two molecules shuttle electrons between the large complexes in the chain.

How many ATPs are generated by this process? Theoretically, for each glucose molecule, 32 ATPs can be produced. As electrons drop from NADH to oxygen

in the chain, the number of protons pumped out and returning through ATP synthase can produce 2.5 ATPs per electron pair. For each pair donated by FADH2, only 1.5 ATPs can be formed. Twelve pairs of electrons are removed from each glucose molecule;
10 by NAD+ = 25 ATPs
2 by FADH2 = 3 ATPs.
Making a total of 28 ATPs. However, 2 ATPs are formed during the Krebs' cycle and 2 ATPs formed during glycolysis for each glucose molecule therefore making a total ATP yield of 32 ATPs. In reality, the energy from the respiratory chain is used for other processes (such as active transport of important ions and molecules) so under conditions of normal respiration, the actual ATP yield probably does not reach 32 ATPs.
The reducing equivalents that fuel the electron transport chain, namely NADH and FADH2, are produced by the Krebs cycle (TCA cycle) and the beta-oxidation of fatty acids. At three steps in the Krebs cycle (isocitrate conversion to oxoglutarate; oxoglutarate conversion to succinyl-CoA; Malate conversion to oxaloacetate), a pair of electrons (2e-) are removed and transferred to NAD+, forming NADH and H+. At a single step, a pair of electrons are removed from succinate, reducing FAD to FADH2. From the beta-oxidation of fatty acids, one step in the process forms NADH and H+ and another step forms FADH2.
Cytoplasmic NADH, generated from glycolysis, has to be oxidized to reform NAD+, essential for glycolysis, otherwise glycolysis would cease to function. There is no carrier that transports NADH directly into the mitochondrial matrix and the inner mitochondrial membrane is impermeable to NADH so the cell uses two shuttle systems to move reducing equivalents into the mitochondrion and regenerate cytosolic NAD+.
The first is the glycerol phosphate shuttle, which uses electrons from cytosolic NADH to produce FADH2 within the inner membrane. These electrons then flow to Coenzyme Q. Complex I is bypassed so only 1.5 ATPs can be formed per NADH via this route. The overall balanced equation, summing all the reactions in this system, is
NADH (cytosol) + H+ (cytosol) + NAD+ (mito.) = NAD+ (cytosol) + NADH (mito.) + H+ (mito.)
The malate-aspartate shuttle uses the oxidation of malate to generate NADH in the mitochondrial matrix. This NADH can then be fed directly to complex I and thus can form 3 ATPs via the respiratory chain. The overall balanced equation is
NADH (cytosol) + H+ (cytosol) + FAD (inner memb.) = NAD+ (cytosol) + FADH2 (inner memb.)
Both of these shuttle systems regenerate cytosolic NAD+.
The entry point for NADH is complex I (NADH dehydrogenase) and the entry point for FADH2 is Coenzyme Q. The input of electrons from fatty acid oxidation via ubiquinone is complicated and not shown in the diagram. ([15], [16], [17], [18], [19],)

III. RESULT & DISCUSSION

• In the presence investigation, genes associated with the lead and receptor molecules were analyzed.In the current investigation, the smiles of molecules are identified using the Pubchem application. By incorporating these smiles into the complex procedure called as "swiss target prediction," uniport ids for the genes and receptors were obtained.
• The present study then found that additional genes were extracted from the 10-gingerol molecule and from the SEA tool using a number of tools, such as Swiss target prediction, Malacards, Omim, and Disgenet.Common genes were also found using an AI technique. The common gene was obtained using Venny 2.1.0.
• After that, sickness pathways were obtained using Reactome software, and centrality metrics in the current were obtained using a string tool from Cytoscape.

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