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Network pharmacology reveals the therapeutic mechanism of *Rubus Idaeus* against ESR1 gene responsible for epilepsy

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ABSTRACT

In this research work, an effort has been made to find the potential synergy of Rubus idaeus for the management of epilepsy through the application of a combination of network pharmacology and molecular docking techniques. The active phytochemicals of Rubus idaeus were searched for with the help of the 'IMPPAT 2.0 and Dr. Duke's Phytochemical & Ethnobotanical Databases'. Similarly, the 'Comparative Toxicogenomics Database (CTD)' was used for generating the molecular targets of the aforementioned phytochemicals of Rubus idaeus, while the 'GeneCards & MalaCards Databases' were used to obtain the genes responsible for the progression of epilepsy. Using the concept of the 'Venn Diagram Approach,' the common genes among Rubus idaeus and genes for epilepsy were obtained, and they represent the potential target genes for the management of the given disease condition. Finally, the interaction of compounds & targets & disease could be generated with the 'Cytoscape Software & CytoHubba,' while the 'STRING Database' was used to obtain the 'PPI-Network'. And the 'functional enrichment,' 'Gene Ontology,' & 'DisGeNET Pathways Analysis,' respectively, were obtained with the help of the 'Metascape Web Server'.

A total of 16 active compounds in Rubus idaeus were discovered, and these targeted 6,744 gene targets. At the same time, a total of 6,251 genes associated with epilepsy were obtained, and their intersection yielded important target genes with the potential of mediating the anti-epileptic properties of Rubus idaeus. These target genes included a major hub gene, estrogen receptor 1 (ESR1), whose importance for the regulation of genes associated with epilepsy was very clear. The molecular docking study also revealed the high binding affinity between alpha carotene and ESR1.

In general, a combined analysis of network pharmacology and molecular docking reveals that Rubus idaeus acts on multi-target and multi-pathway to exert anti-epileptic activities, which indicates its potential in the management of epilepsy.

Keywords: Network pharmacology, *Rubus idaeus*, Epilepsy, Molecular docking, ESR1.

INTRODUCTION

Raspberries are one of the most popular berries in the world and have a long history of consumption as a food as well as for their medicinal uses [1]. Rubus idaeus, commonly known as the red raspberry, is a perennial herb that comes in the Rosaceae family. Rubus is native to the Ida Mountains in Turkey and has distributed to the rest of the world in Europe and other temperate areas. Rubus is one of the most important genera in the botanical world as it consists of over 740 species that are assigned to 15 subgenera. Idaebetus consists of raspberries. Raspberries get their distinct red color due to the presence of anthocyanin pigments that are also responsible for the blue and purple color of other berries in the world. The unique antioxidants in the fruit are a combination of anthocyanin and other phytochemicals [2,3].

In addition to their agreeable taste and ornamentality, raspberries are valuable sources of key nutrients, such as dietary fiber, carbohydrates, proteins, fatty acids, vitamins, and minerals, essential for proper physiological functions in both humans and

animals. Besides its nutritional values, Rubus idaeus has also been widely employed in folk and traditional medicine all over the world. Leaves and fruits have traditionally been used in remedies for various conditions: fever, influenza, diabetes, gastrointestinal disorders, and cardiovascular diseases [4]. Furthermore, the leaves have sudorific, anti-inflammatory, and antibacterial actions and are very frequently applied topically during the treatment of wounds, inflammation, and infections. The multiplicity of pharmacological activities attributed to Rubus idaeus indicates multiple bioactive compounds showing polypharmacology behaviour, thus enabling their interaction with a wide range of biological targets [13,14]. Epilepsy is a chronic, non-communicable neurological condition that currently affects about 50 million people worldwide. This makes epilepsy one of the most frequent serious central nervous system diseases [5-10]. This condition is identified by recurrent, unprovoked seizures due to abnormally and excessively high electrical discharges in a set of neurons within a person's brain. These seizures may occur in various ways. These may range from a brief loss of attention or a small muscular jerk to more serious and prolonged attacks that happen with loss of consciousness and loss of control over functions like bowel and bladder functions. The occurrence of seizures may happen from a few times a day to a few occurrences in a year. Notably, a seizure episode alone does not define epilepsy, but when a person has two or more unprovoked seizure episodes [6,7].

Despite advances in neuroscience and pharmacology, epilepsy remains difficult to manage in a large proportion of patients. Among the various AEDs in current practice, nearly one-third of patients fail to gain adequate seizure control and may suffer from other adverse side effects, including sedation, cognitive impairment, mood disorders, and liver toxicity [11,12]. The need for safer and more effective therapeutic strategies is, therefore, urgently needed. In recent years, there has been increasing interest in natural products and plant-derived compounds as promising sources of novel anti-epileptic agents because of their chemical diversity, multi-target actions, and relatively favourable safety profiles [9,10].

In contrast to conventional single-target drugs, herbal medicines work via multiple bioactive compounds targeting multiple molecular targets or biological pathways jointly. Based on the complexity of herbal medicines as multi-target/multi-pathway drugs, traditional pharmacological analysis is not adequate to elucidate the mechanisms of action of these formulations. This situation led to the advent of "network pharmacology" as an effective tool describing the integrated actions of pharmacology, bioinformatics, and systems biologists to comprehend the intricate associations between drugs and targets as well as between targets and diseases. Network pharmacology allows the generation of an "interaction network" describing the associations among phytochemicals and their target proteins, as well as the involvement of genes related to the targeted diseases [15,16]. Network pharmacology can be used, in a specific manner, for the identification of regulatory genes and pathways that are involved in modulating diseases using natural products [17]. It can be utilised for the purpose of repositioning drugs, predicting synergy, and exploring new targets for drugs. By providing a platform for the analysis of big data, network pharmacology helps in understanding, holistically, the molecular mechanism through which herbs work [17].

On the other hand, molecular docking has emerged as an essential computer-aided platform in drug development and mechanistic analysis. Molecular docking predicts binding interactions at the atomic level between small molecules (ligands) and target proteins. It facilitates the calculation of the preferred ligand orientation, position, and binding affinity in the active sites of proteins. With the integration of network pharmacology and molecular docking, identification of key target proteins as well as the binding possibility of Bioactive molecules with target proteins, can be achieved.

In the current study, we attempted to utilise an integrated strategy of pharmacology networks and molecular docking simulations to investigate the anti-epilepsy activity of Rubus idaeus. Specifically, we attempted to elucidate the active phytochemical ingredients within Rubus idaeus, the targets of these ingredients, and the genes related to epilepsy that could be influenced by the active ingredients. With the formation of compound-target-disease networks and protein-protein interaction analyses, we attempted to elucidate the regulatory genes and pathways participating in the occurrence of epilepsy [18, 19]. On the other hand, molecular docking was utilised to confirm the binding capacity of the major active ingredients in Rubus idaeus with the key epilepsy-related targets. With the current comprehensive approach, the study endeavours to provide mechanistic evidence to illustrate the effectiveness of Rubus idaeus as a multi-target drug in the treatment of epilepsy [20].

MATERIALS AND METHODS

Screening of drug active ingredients

The Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0 (IMPPAT 2.0) and Dr. Duke's Phytochemical and Ethnobotanical databases were used to determine the active compound of *Rubus idaeous* [21].

Collection of active compound targets

From the Comparative Toxicogenomic Database (CTD), the active compound gene was searched, and the duplicated genes were deleted.

Figure 1: Flowchart representing the complete study of the methodology

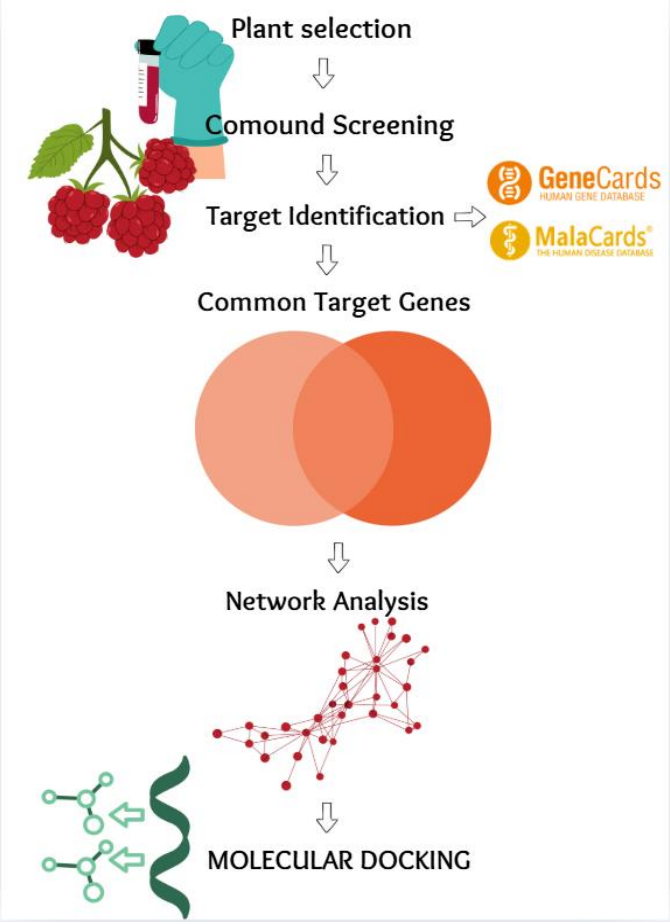


Table 1: Information about the software and databases used in the experiment

Name	Website
IMPPAT 2.0 (Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0)	https://cb.imsc.res.in/imppat/
Dr. Duke's Phytochemical and Ethnobotanical Databases	https://phytochem.nal.usda.gov/phytochem/search
CTD (Comparative Toxicogenomic Database)	http://ctdbase.org/
MalaCards	https://www.malacards.org/
Gene Cards	https://www.genecards.org/
Bioinformatics & Evolutionary Genomics (Venn Diagram)	https://bioinformatics.psb.ugent.be/webtools/Venn/
STRING database	https://string-db.org/
Cytoscape 3.9.1	https://cytoscape.org/
CytoHubba	https://apps.cytoscape.org/apps/cytohubba
Metascape	https://metascape.org/gp/index.html#/main/step1
PubChem	https://pubchem.ncbi.nlm.nih.gov/
RCSB Protein Data Bank (RCSB PDB)	https://www.rcsb.org/
DockThor	https://dockthor.lncc.br/v2/
Discovery Studio	https://discover.3ds.com/discovery-studio-visualizer-download

Collection and acquisition disease target

Mala Cards and Gene Cards were used to search for the genes associated with epilepsy [22], and duplicate genes were eliminated. Then the Venn diagram tool was used to identify the common gene between Rubus idaeous and Epilepsy (Figure 1) [26].

Establishing the protein–protein interaction (PPI) network

The protein-protein interaction (PPI) network diagram of the Rubus idaeous gene target for the treatment of epilepsy was created after the common gene target were imported into STRING database, which the plugin of Cytoscape 3.9.1, in the form of gene symbols. Homo sapiens was chosen as the species, and PPI was selected with a confidential value of 0.95 [23].

Construction of the network

The association between Rubus idaeous and epilepsy was then depicted using a network map of drug and disease targets created with Cytoscape software (version 3.9.1) [24]. The genes with the highest degree of interaction were then found using CytoHubba [27].

Metascape enrichment analysis of common targets of rubus idaeous and epilepsy

The Metascape tool is used for functional enrichment analysis of common gene targets, in which GO enrichment analysis and Dis Ge Net enrichment analysis were used, in which the top 20 genes are selected for analysis [25].

Molecular docking

The structure of protein receptor was downloaded from Protein data bank (PDB) in PDB file format, and its attached ligands, heteroatoms, and water molecules were removed before docking then the 3D structure of the ligand was downloaded from PubChem and converted into PDF file format by using Discovery studio [28,29]. Then the obtained protein structure and ligand structure docked and visualised by DockThor and the individual docking scores of each component were recorded and the poorer binding scores for each component were noted against epilepsy [30].

RESULT

Assortment of drug active ingredients

The active ingredient of Rubus idaeous compounds was retrieved using the Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0 (IMPPAT 2.0) and Dr. Duke's Phytochemical and Ethnobotanical databases, and efficient compounds were discovered. 16 possible active components were found for Rubus idaeous (Table 2). [31, 34].

Table 2: Potential active ingredients of Rubus idaeous

Name	Molecular Formula
1-Hexanol	$C_6H_{14}O$
Benzaldehyde	C_7H_6O
2-Hexenal	$C_6H_{10}O$
Quercetin	$C_{15}H_{10}O_7$
Beta-Sitosterol	$C_{29}H_{50}O$
1-Pentanol	$C_5H_{12}O$
(+)-Catechin	$C_{15}H_{14}O_6$
(-)-Epicatechin	$C_{15}H_{14}O_6$
Beta-Carotene	$C_{40}H_{56}$
Beta-Ionone	$C_{13}H_{20}O$
Calcium	Ca^{+2}
Acetoin	$C_4H_8O_2$
Alpha-Carotene	$C_{40}H_{56}$
Alpha-Tocopherol	$C_{29}H_{50}O_2$
Aluminum	Al
Boron	B

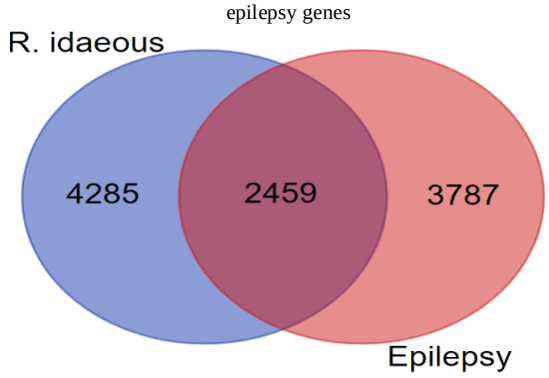
Gene Target Collection of *Rubus idaeous*

A total of 13,679 gene targets were gathered from 16 putative active components of Rubus idaeous using the Comparative Toxicogenomic Database (CTD) [32,33]. The list was then updated without the redundant gene targets. A total of 6744 gene targets were identified after the duplicate gene targets were eliminated.

Collection of disease-related targets

By using MalaCards and Gene Cards, we have obtained the gene target of epilepsy. In which we have obtained 6,250 gene from Gene Cards and 315 genes from Mala Card, the total number of genes for epilepsy we have obtained is 6,565 genes. After removing duplicated genes, we have obtained a total 6,251gene target of epilepsy. The active component of Rubus idaeous regarding diseases was matched to eliminate the shared targets, leading to in 2459 common targets (Figure 1). Then, 2459 overlapped targets were found; they were referred to as intersecting targets of Rubus idaeous and epilepsy [34-37].

Figure 2: Venn diagram showed the intersection of Rubus idaeous and epilepsy genes



Result of PPI network construction

The 2459 common gene targets were placed into the STRING database [38] which is the plugin of Cytoscape [39] 3.9.1 for analysis to create the PPI network. This network graph has 2433 nodes overall, 6820 edges, with an average node degree value of 9.5 and the confidential score is 0.95 after the free points were hidden. In this case, the edges denote a protein-protein interaction link whereas the nodes represent proteins. The stronger the link, the more lines there are. The file that was downloaded from the string was then processed to create a table (Table 3) based on the value of the degree. ESR1 has the greatest degree (degree=15) of the PPI core gene targets, which also highlights the significance of the gene target in the epilepsy effect of *Rubus idaeous*.

Identification of hub gene

The PPI interaction network was imported into CytoHubba [40], which is a plugin of Cytoscape, to construct the drug-active ingredient-target-disease network diagram (Figure 2). After analysing, it was found that ESR1 had the most targets, which were represented with blue colour.

Metascape enrichment analysis

The Metascape tool is used for functional enrichment analysis of 2459 common genes targets, GO enrichment analysis (Figure 3) was used to learn about the gene and their pathway some of the neurological pathway are like Pathways in cancer and Pathways of neurodegeneration - multiple diseases and then DisGeNet enrichment analysis (Figure 4) was used to learn about the role of the gene in other diseases in this the neurological disease are, Hepatitis, Presenile dementia, Transient Ischemic Attack, Brain Ischemia and Down Syndrome, the top 20 genes are selected for analysis. [41-52].

Figure 3: Drug-active ingredient-target-disease network

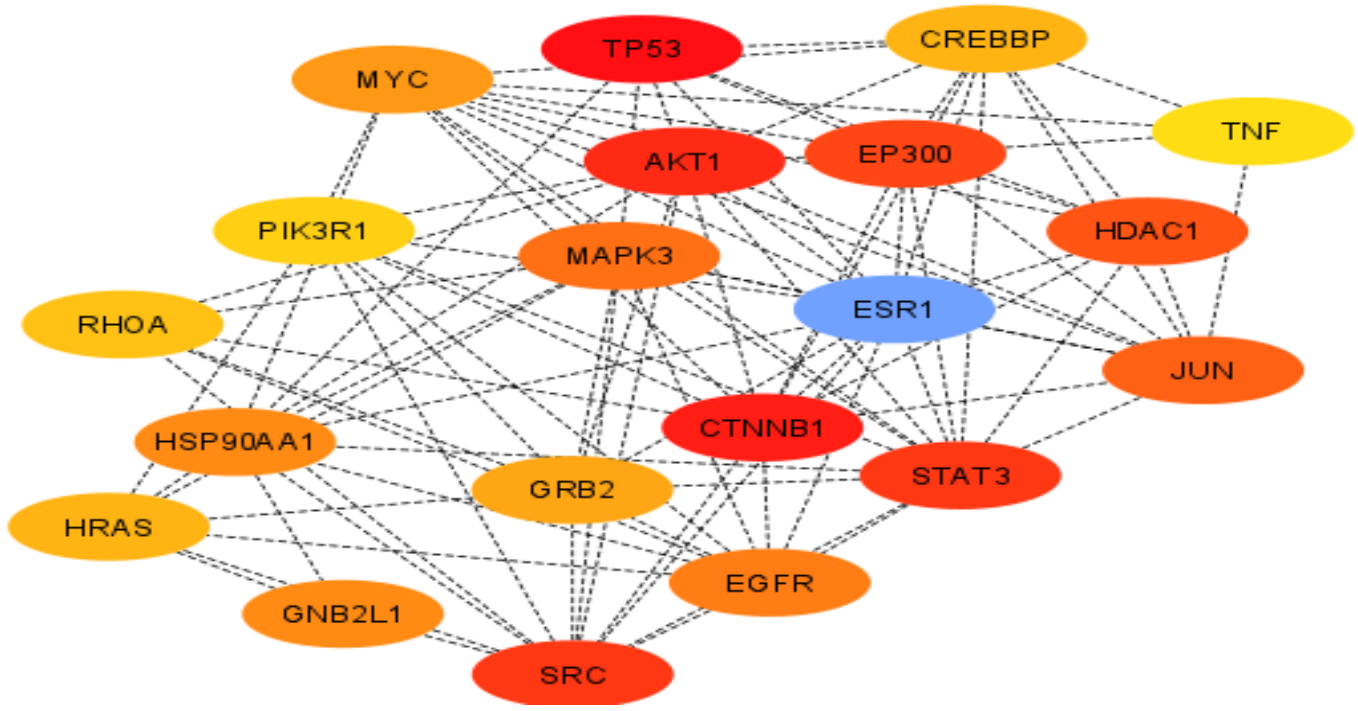


Figure 4: GO functional enrichment analysis results

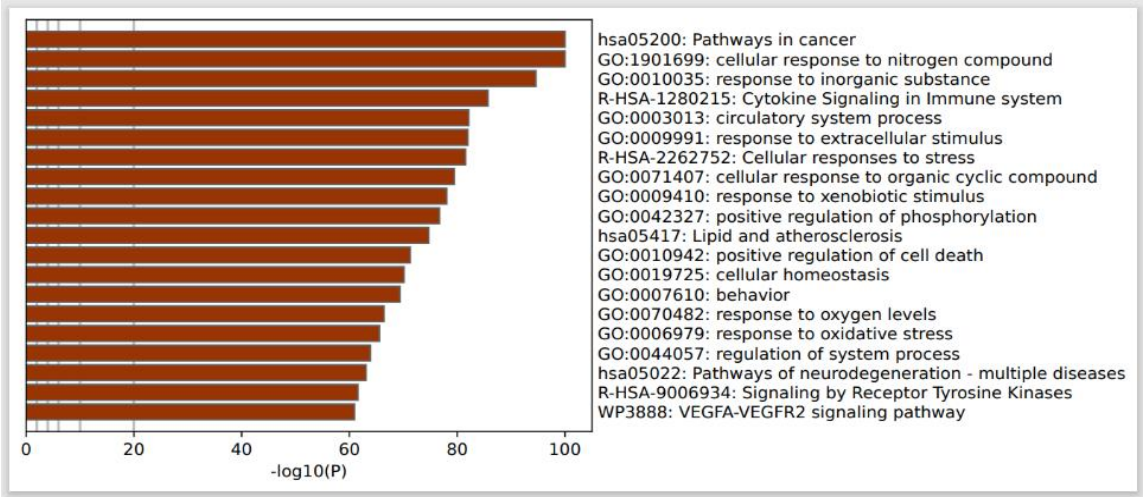


Figure 5: Dis Ge Net enrichment analysis results

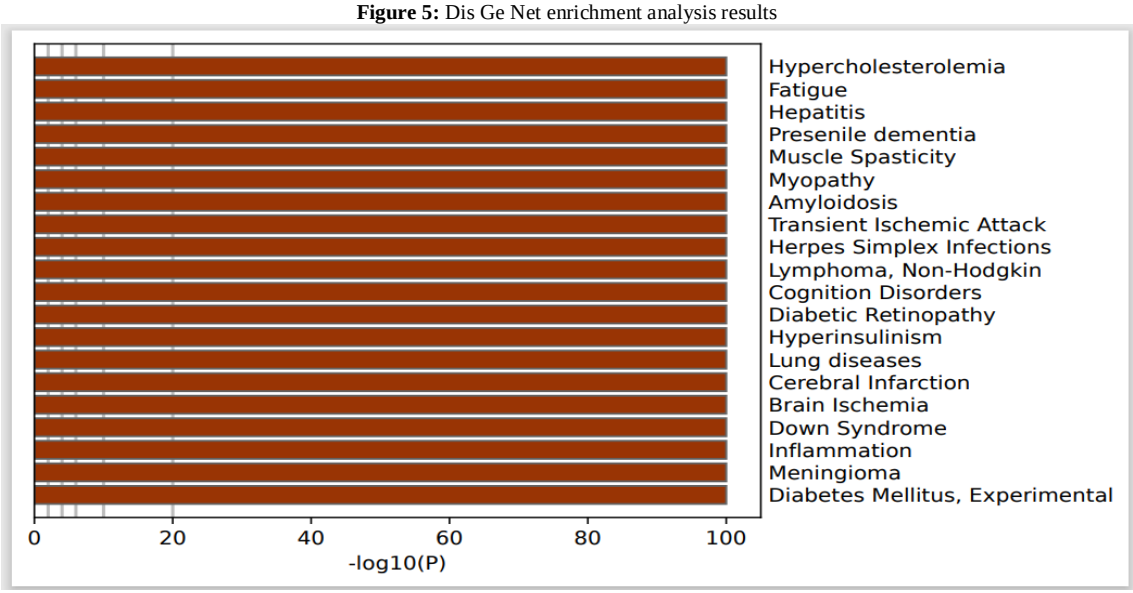


Figure 6: Docking of ESR1 with ALPHA-CAROTENE

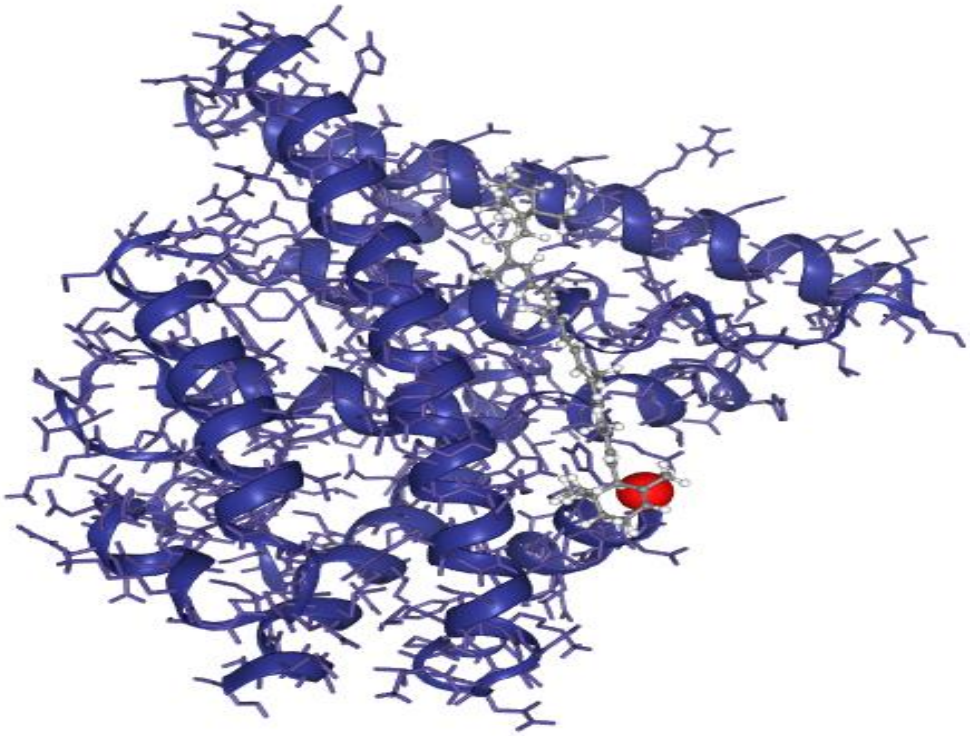


Table 4: Binding energy of molecular docking (kcal/mol).

Ligand	Binding Energy
Beta-Sitosterol	-8.020 kcal/mol
1-Pentanol	-6.943 kcal/mol
(+)-Catechin	-7.147 kcal/mol
(-)-Epicatechin	-6.732 kcal/mol
Beta-Carotene	-9.000 kcal/mol
Beta-Ionone	-8.696 kcal/mol
Calcium	-5.886 kcal/mol
Acetoin	-6.252 kcal/mol
Alpha-Carotene	-9.225 kcal/mol
1-Hexanol	-7.131 kcal/mol
Benzaldehyde	-6.489 kcal/mol
2-Hexenal	-6.438 kcal/mol
Quercetin	-6.798 kcal/mol
ALPHA-TOCOPHEROL	-8.642 kcal/mol

CONCLUSION

"A network pharmacology strategy was established to investigate the complex, multi-target, and multi-pathway effective capabilities of Rubus idaeus in the treatment of epilepsy. With the help of databases concerning the interaction of compound-target and disease-target, sixteen active compounds in Rubus idaeus have been found, a set of 6,744 potential gene targets for epilepsy. "From the screened compounds, such as 1-hexanol, benzaldehyde, 2-hexenal, quercetin, and α-carotene, some were found to exhibit a high connection with molecular pathways for epilepsy. α-Carotene, discovered and isolated as one of the most successful compounds, falls in the category of provitamin A carotenoids, capable of being converted into retinol in the human body. It is the second most widely available carotene after β-Carotene and can easily be derived from yellow-orange, as well as green, vegetables like carrots, pumpkins, and sweet potatoes, and spinach, broccoli, and lettuce, respectively. Biochemically, alpha carotene is broken down into biologically active vitamin A, and its properties include being an antioxidant, an immune modulator, and having neuroprotection capabilities as well.

In addition to PPI network analyses, Cytoscape-based topology analyses identified a set of hub genes that could be potentially involved in the anti-epileptic properties of Rubus idaeus. These genes include MYC, TP53, TNF, SRC, MAPK3, AKT1, HRAS, JUN, CTNNB1, and ESR1. Of all these genes, estrogen receptor alpha (ESR1) was a hub gene with a significant role in regulation. Indeed, ESR1 encodes a nuclear hormone receptor. Upon binding to its ligand, estrogen, the receptor is a transcription factor that controls genes related to neural signalling, synaptic functions, inflammation, or neuroprotection. An imbalance in an estrogen pathway has already been implicated in seizure susceptibility and epilepsy. The molecular docking study reinforced these results by showing that there are high binding affinities between ESR1 and diverse compounds derived from Rubus idaeus, especially α-carotene, β-carotene, β-ionone, and α-tocopherol. The ligands had a stable binding complex with the binding pocket of ESR1, which is supported by the binding energy and hydrogen bonding, indicating that the ligands can modulate the signal transduction pathways mediated by ESR1.

The integrated analysis conducted between pharmacology and molecular docking proves that Rubus idaeus possesses anti-epileptic activities via multi-target regulation, in which ESR1 is found to play an essential part. Of identified active compounds, α-carotene is found to be one of the promising drug candidates that likely explain its potency as an alternative multi-target drug to treat epilepsy.

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