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Cucumis Melo's Bioactives for Treatment of Epilepsy: A Systematic Investigation of Network Pharmacology and Molecular Docking

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Abstract: One of the oldest and most prevalent severe brain diseases is epilepsy. *Cucumis melo* is a member of the *Cucurbitaceae* family, which is used in traditional medicine to treat a variety of illnesses. The ultimate goal of this study was to examine the active constituents and mechanisms of CM against epilepsy using network pharmacology along with molecular docking technique. The chemicals in CM were determined by a review of the literature as well as the IMPPAT database. The resulting compounds were then analysed using the ADMET method. Subsequently, the STRING database was employed to design networks using the found common genes, and CB-Dock2 software was applied for docking. Out of 145 active components in CM, only 11 compounds shown outstanding potential biological activity during ADMET screening. Additionally, by accessing a number of public databases, we were able to identify 8093 genes for target chemicals and epilepsy, respectively. The results of the compounds-target network research showed that the 152 interconnected genes and 11 compounds that make up the key components and gene targets of CM against epilepsy are Eubricol and AKT1, the most prominent active component and hub protein, respectively. The metabolic pathway, reaction to xenobiotic stimulus, essential component of plasma membrane, enzyme binding, and tumour necrosis factor alpha pathways were shown to be of greatest importance based on pathway enrichment assessment. According to a molecular docking investigation, tirucallol, euphol, and eburicol demonstrated notable glide scores. Initially, we used network pharmacology and molecular docking to examine the molecular mechanisms and active components of CM for epilepsy. Our research offers empirical evidence that could bolster the medical advantages of CM; nonetheless, additional confirmation of active molecules in epilepsy treatment is necessary.

Keywords: *Cucumis melo, Cucurbitaceae,* Epilepsy, STRING, CB-Dock2 software, ADMET and Network Pharmacology

Introduction

Epilepsy affects over 70 million individuals worldwide and is considered one of the most prevalent and severe neurological conditions. An "enduring propensity of the nervous system to trigger epileptic seizures, with neurobiological, cognitive, psychological, and social consequences" is the theoretical description of epilepsy [1]. Despite the availability of over 20 antiepileptic medications, about one-third of patients remain resistant to treatment, highlighting a critical treatment gap [2]. Individuals with epilepsy also face a higher prevalence of comorbid conditions such as depression, anxiety, dementia, and migraines, which further exacerbate their burden [3]. This underscores the need for novel therapeutic approaches, including the exploration of plant-based treatments like *Cucumis melo* (CM), which exhibit mechanisms such as GABAergic enhancement, modulation of ion channels, and neuroprotective effects [4].

Network pharmacology and molecular docking are modern computational tools that have revolutionized drug discovery. Network pharmacology, which integrates systems biology and computational methods, enables the construction of "protein-compound/disease-gene" networks to study multi-target drug interactions [5]. This approach shifts the paradigm from single-target therapies to multi-component treatments, offering a promising framework for studying botanical compounds like CM. Molecular docking, on the other hand, predicts the binding interactions between drug molecules and their targets, aiding in the identification of high-affinity lead compounds [6]. Together, these tools provide a robust platform for exploring the therapeutic potential of CM in epilepsy (Figure 1).

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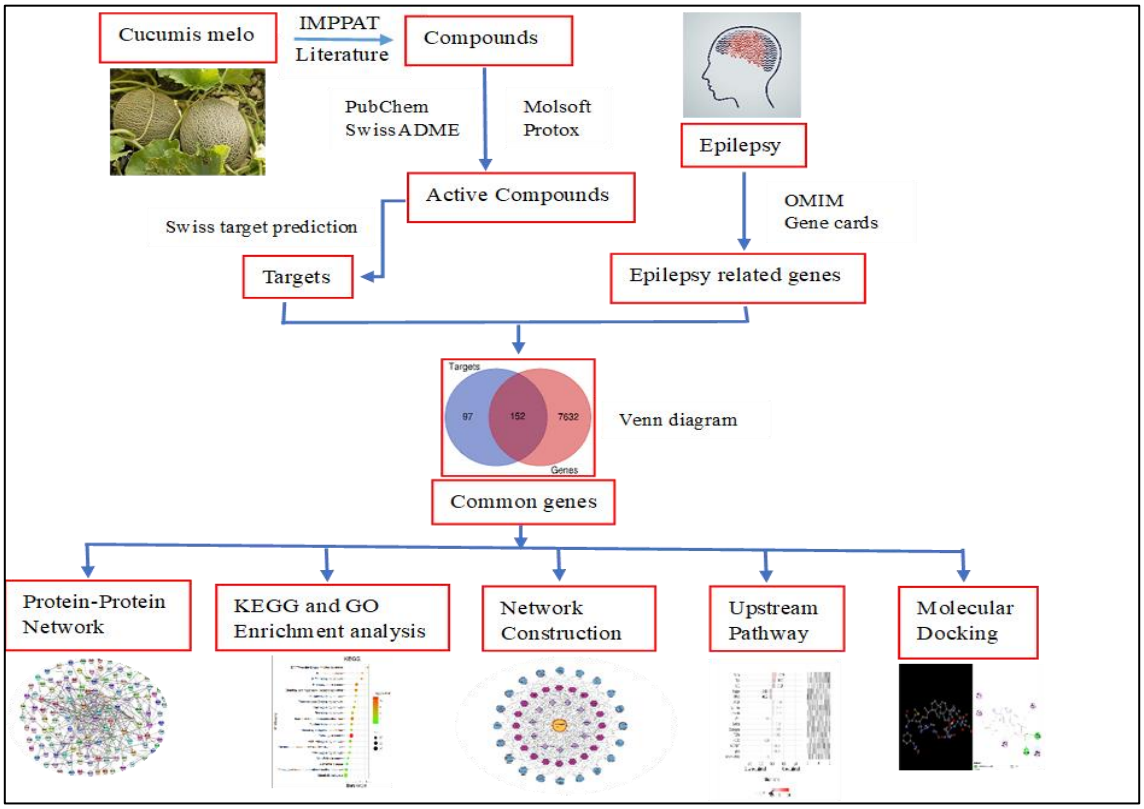


Figure (1): Structured methodology used for Network Pharmacology and Molecular Docking.

Musk melon, scientifically known as *Cucumis melo* and referred to as kharbuzah in Unani herbal medicine [7], belongs to the genus Cucurbitaceae. It has been traditionally used to treat a variety of ailments, including renal stones, gastrointestinal disorders, and metabolic conditions [8]. Given its historical therapeutic applications and potential mechanisms of action, CM emerges as a promising candidate for further investigation in epilepsy management.

Methods

Identification of Potential Compounds

We obtained the chemical components of *Cucumis melo* from the online database of Indian medicinal plants, phytochemistry, and therapeutics (IMPPAT) [9]. The PubChem database was queried to determine the Compound ID (CID) and Canonical Simplified Molecular-Input Line-Entry System (SMILES) of the identified active compounds [10]. To ensure data reliability, only compounds with well-documented pharmacological profiles were selected.

Screening of Bioactive Substances

The canonical SMILES of the collected compounds were uploaded to the SwissADME platform to determine their molecular mass and bioavailability scores. Drug-likeness (DL) scores were calculated using Molsoft Software, with compounds scoring above 0.18 for both DL and bioavailability considered for further analysis [11, 12**].** This threshold was chosen based on established literature indicating optimal pharmacological activity for compounds meeting these criteria. Toxicity profiles, including carcinogenicity, immunogenicity, mutagenicity, and cytotoxicity, were predicted using ProTox-II [13]. Compounds with high toxicity risks were excluded to ensure safety.

Identification of Potential Compound Targets

Swiss Target Prediction was used to predict the targets of the bioactive components, restricted to the species *Homo sapiens*. The canonical SMILES of each compound were entered into the platform. To ensure reproducibility, all steps were documented, and raw data were archived for future reference.

Two databases were used to retrieve epilepsy-related genes:

1. GeneCards (the Human Gene Database)**:** A comprehensive database of annotated and predicted human genes [14, 15].
2. OMIM (Online Mendelian Inheritance in Man)**:** A database known for its focus on the genetic basis of diseases [16].

Searches for "epilepsy" were conducted in both databases, and the resulting gene lists were merged. Overlap analysis was performed using the Bioinformatics and Evolutionary Genomics database to identify potential therapeutic targets [17]. A Venn diagram was generated to visualize the overlapping genes, ensuring transparency in target selection.

Enrichment Analysis

Gene Ontology (GO) Enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment analyses were performed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID). DAVID was chosen for its robust analytical tools and comprehensive biological information repository. Advanced bubble charts were generated using the SRPLOT web-based tool. To ensure accuracy, enrichment results were cross-verified with other databases such as Enrichr.

Upstream Pathway Activity Analysis

SPEED2 was utilized to identify upstream pathway activity involving *Cucumis melo* and epilepsy-related genes with shared regulatory components. This step was critical for understanding the transcriptomic modulation mechanisms underlying epilepsy.

Protein-Protein Interaction (PPI) Analysis

The Search Tool for the Retrieval of Interacting Genes (STRING) database was used to analyze protein-protein

interactions (PPIs). The combined gene list was input into STRING, restricted to *Homo sapiens*, with a confidence score threshold of 0.7. This threshold was selected to balance specificity and sensitivity in PPI identification. The resulting network was imported into Cytoscape 3.7.1, and the top 20 hub proteins were identified using the cytohubba plugin and degree score method [18]. Raw interaction data were archived to facilitate reproducibility.

Network Construction

Three distinct networks were constructed using Cytoscape:

1. Compound-Potential Target (C-T) Network**:** Linking compounds to their potential targets in epilepsy.
2. Target-Pathway (T-P) Network**:** Linking targets to pathways from KEGG.
3. Herb-Compound-Target-Pathway Network**:** Integrating compounds, targets, and pathways.

Nodes represented candidate compounds, targets, and pathways, while edges depicted their interactions [19, 20]. To enhance clarity, simplified visual representations of the networks were included in the supplementary materials.

Molecular Docking

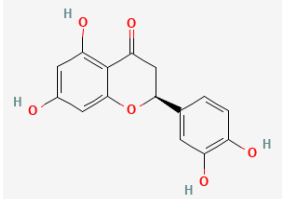
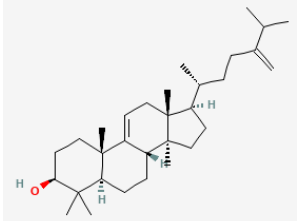
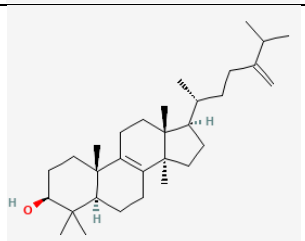
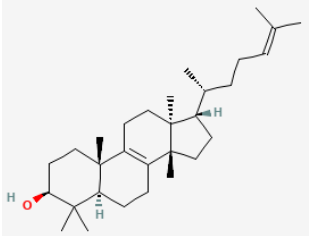
Molecular docking was performed using CB-Dock2 to analyze the binding affinity of key target proteins and candidate compounds. The CB-Dock2 tool was selected for its accuracy in predicting binding poses and affinity scores. Compound data in 2D SDF format and protein data in PDB format were retrieved from PubChem and RCSB, respectively. Docking scores were recorded, and docking positions were visualized using Discovery Studio. To ensure reproducibility, docking parameters and raw data were documented and made available as supplementary files.

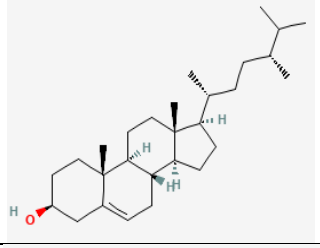
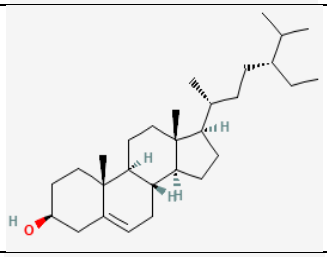
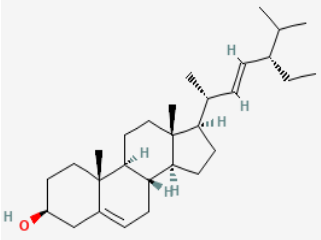
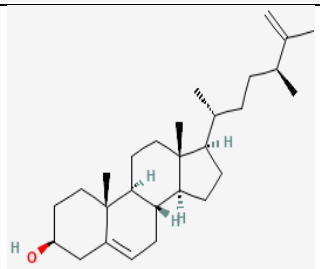
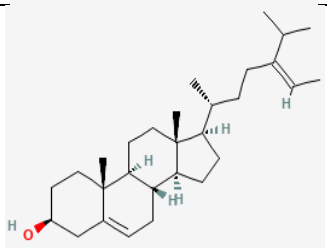
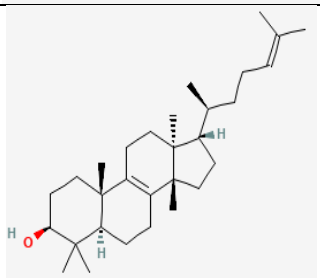
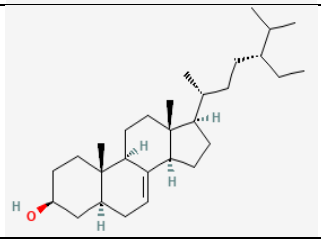
Results and Discussion

Locating and Evaluating Potential Bioactive Substances

By combining literature searching and database searches, we identified an aggregate of 145 compounds in CM. We evaluated the druggability of each candidate using the OB and DL indices. When designing bioactive compounds for use as therapeutics, it is typically crucial to account for their high OB values. During the drug design phase, the pharmacodynamic and pharmacokinetic characteristics of a molecule determine its drug-likeness (DL) and its ADME features. Only 19 of the 145 compounds in CM met the criteria of having a DL of 0.18, an OB of 0.3, and having undergone toxicity testing [21]. After removing the counterfeits, 11 compounds remained, all of which exhibited potential as active ingredients (Table 1). A lot of the active ingredients that were chosen are sterols, such as 24-methylene-24-dihydroparkeol, eburicol, eupholcampesterol, beta-sitosterol, stigmasterol, codisterol, fucosterol, tirucallol, schottenol, and flavonoids, such as eriodictyol. The researchers observed that flavonoids, sterols, and triterpenoids exhibit anticonvulsant activity and may enhance the action of the GABA receptor [22]. Therefore, they may be useful chemicals for treating epilepsy and other central nervous system conditions [23].

Table (1): The potential active compounds of CM.

CID	Compound	Molecular structure	Drug Likenesss	Oral bioavailability	Herb
440735	Eriodictyol		0.96	0.55	CM
489917	24-Methylene-24-dihydroparkeol		0.26	0.55	CM
9803310	Eburicol		0.32	0.55	CM
441678	Euphol		0.55	0.55	CM

CID	Compound	Molecular structure	Drug Likenesss	Oral bioavailability	Herb
173183	Campesterol		0.59	0.55	CM
222284	beta-Sitosterol		0.78	0.55	CM
5280794	Stigmasterol		0.62	0.55	CM
13833114	Codisterol		0.43	0.55	CM
5281328	Fucosterol		0.85	0.55	CM
101257	Tirucallol		0.55	0.55	CM
441837	Schottenol		0.18	0.55	CM

Targets associated with the compounds and genes associated with Epilepsy

100 targets were taken for each compound from the Swiss target prediction. 8093 genes were obtained by combing the genes from Gene cards and OMIM databases (Table 2). Through the venn diagram we have got 97targets, 7632 genes and 152 combined genes (Figure 2).

Table (2): Docking results of active compounds with Targets.

Sr. no	Compound	Protein	Glide score
1	Eriodictyol	Estrogen receptor beta	-8.6
2	24-Methylene-24-dihydroparkeol	Acetylcholinesterase	-7.9
3	Eburicol	Dual specificity phosphatase	-9.3
4	Euphol	Cytochrome P450 17A1	-9.1
5	Campesterol	Sterol regulatory element-binding protein 2	-7.3
6	beta-Sitosterol	Sterol regulatory element-binding protein 2	-7.7
7	Stigmasterol	MAP kinase ERK1	-8.4
8	Codisterol	11-beta-hydroxysteroid dehydrogenase 2	-8.4
9	Fucosterol	Anti-estrogen binding site (AEBS)	-8.7
10	Tirucallol	Cytochrome P450 17A1	-9.1
11	Schottenol	protein kinase C eta	-6.7

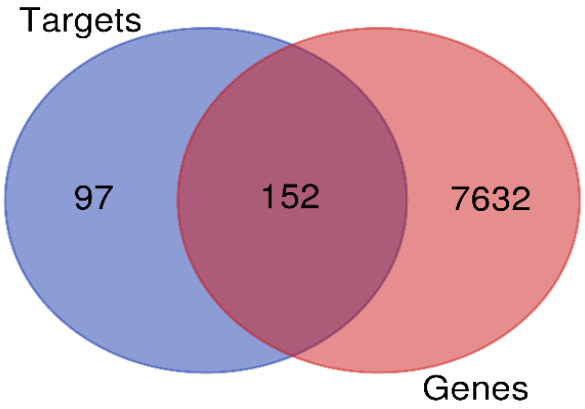


Figure (2): Venn diagram showing common genes between Epilepsy-related genes and CM targets.

Enrichment analysis

The classification of enriched GO keywords takes place at the levels of BP (biological process), CC (cellular component), and MF (molecular function). The KEGG database enables large-scale studies of networks of interactions between genes and proteins (Table 3). We used the web-based DAVID programme to investigate the role of 152 shared targets between CM compounds and epilepsy.This helped us figure out how the medicine might work by finding over-represented GO terms and KEGG pathways with P<0.05 and count-largest to smallest. We gathered a total of 572 enrichment findings after analysing GO enrichment. In total, there are 401 BP, 66 CC, and 105 MF. We plotted the seven most important pathway GO keywords on a graph (Figure 3).

Table (3): The top three KEGG pathways and their associated genes.

KEGG ID	Terms	Count	P-value	Associated genes
hsa01100	Metabolic pathways	45	1.40E-04	PFKFB3, MAOB, ODC1, HMGCR, CYP2C19, ATP12A, CYP3A4, PTGS2, PLA2G7, CYP19A1, CYP17A1, HSD11B2, CA1, EBP, STS, CA5B, CA3, CA2, CA5A, HSD17B1, HSD17B2, CA4, CA7, CA6, CA9, ACP1, CA13, ST3GAL3, FDFT1, CA12, G6PD, NOS2, DGAT1, EPHX2, PDE4D, PLA2G2A, GCK, SIRT2, CYP24A1, CYP11B1, DHCR7, UGT2B7, MGLL, PTGES, IDO1
hsa05200	Pathways in cancer	35	5.46E-12	ALK, CSF1R, PTGER3, PTGS2, HIF1A, EGFR, IGF1R, SHH, TERT, AKT1, MAPK3, PRKCG, NOS2, PRKCB, MMP2, F2, MMP9, ESR1, PGF, ESR2, VEGFA, AR, CDK6, RPS6KB1, CDK4, KIT, CDK2, BCL2, MDM2, AGTR1, PPARG, MET, FGFR1, BCL2L1, PPARD
hsa04080	Neuroactive ligand receptor interaction	26	1.57E-09	CHRM3, OXTR, CHRM1, CHRNA7, NPY2R, PTGER3, OPRL1, PLG, NR3C1, CRHR1, GRM2, GLRA1, GRM5, CNR2, CNR1, ADORA1, DRD2, DRD3, GABBR1, NPY5R, AVPR2, TACR1, AVPR1A, OPRM1, F2, AGTR1

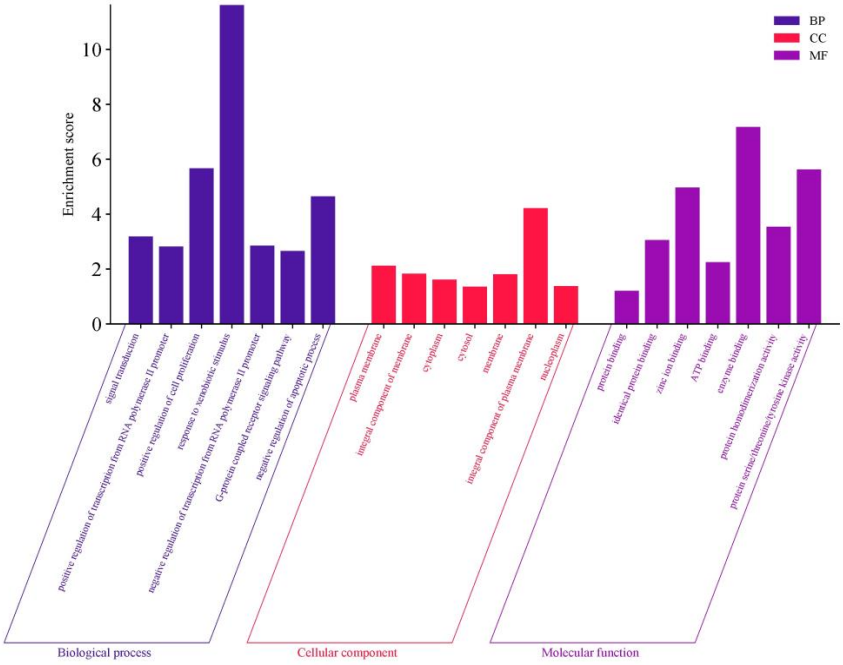


Figure (3): Gene Ontology (GO) Enrichment Analysis of Target Genes.

Through the ranking of GO BP, it was shown that a significant response to xenobiotic stimulus and positive regulation of cell proliferation through the CC integral component of the plasma membrane and plasma membrane, MF enzyme binding, and protein serine, /threonine/tyrosine kinase activity were the most significant (Table 4).

Table (4): Gene ontology (BP, CC, MF)-the top three pathways and their associated genes.

GO ID	Term	Count	P Value	Associated genes
GO:0009410	Response to xenobiotic stimulus	23	4.38E-17	BCHE, ABCC1, OXTR, ABCB1, MAOB, SRC, MMP2, PTGS2, SLC6A2, TNF, SLC6A3, PGF, SLC6A4, HSD11B2, RPS6KB1, CDK4, BCL2, CA9, PPARG, TOP1, DRD2, DRD3, SNCA
GO:0008284	Positive regulation of cell proliferation	24	3.41E-11	CSF1R, CHRNA7, INSR, AVPR2, ODC1, AVPR1A, F2, EGFR, PGF, IGF1R, VEGFA, AR, SHH, CDK4, CXCR3, KIT, CDK2, MDM2, KDR, BCL2, AKT1, DRD3, FGFR1, BCL2L1
GO:0043066	Negative regulation of apoptotic process	19	1.34E-07	CSF1R, NPY5R, SRC, TNF, MMP9, EGFR, IGF1R, VEGFA, SHH, RPS6KB1, MDM2, ADORA1, KDR, BCL2, AKT1, DRD3, BCL2L1, PPARD, SNCA
GO:0005887	Integral component of plasma membrane	45	1.30E-16	ALK, CSF1R, APP, CHRM3, OXTR, CHRM1, CHRNA7, NPY2R, PTGER3, OPRL1, SLC6A2, TNF, SLC6A3, EGFR, CRHR1, SLC6A4, IGF1R, GRM2, GLRA1, GRM5, CNR2, CNR1, CXCR3, ADORA1, KDR, FFAR1, DRD2, DRD3, CCR1, KCNH2, ABCC1, GABBR1, NPY5R, INSR, GPR55, AVPR2, TACR1, AVPR1A, OPRM1, BACE1, KIT, AGTR1, MET, GPR18, FGFR1
GO:0005886	Plasma membrane	84	4.05E-14	ALK, ACHE, APP, CHRM3, OXTR, CHRM1, NPY2R, SERPINE1, ATP12A, SLC6A2, TNF, SLC6A3, SLC6A4, IGF1R, GRM2, SHH, GRM5, STS, CA2, CA4, ADORA1, KDR, AKT1, CA9, FFAR1, KCNH2, PRKCG, ABCC1, NPY5R, DGAT1, PRKCB, PDE4D, MMP2, AVPR2, PRKCD, AVPR1A, TACR1, OPRM1, F2, SIRT2, DNM1, BACE1, BACE2, AR, KIT, AGTR1, PGR, MAPT, MET, MGLL, ABCG2, CSF1R, ABCB1, SRC, CHRNA7, PTGER3, OPRL1, PLG, CYP2C19, EGFR, CRHR1, GLRA1, TERT, CNR2, CNR1, CXCR3, DRD2, DRD3, MAPK3, SNCA, CA12, CCR1, PTPN1, BCHE, GABBR1, NOS2, INSR, PLA2G2A, GPR55, ESR1, MDM2, PTPN2, GPR18, FGFR1
GO:0016021	Integral component of membrane	73	1.44E-08	ALK, ACHE, APP, OXTR, FAAH, ATP12A, SLC6A2, TNF, SLC6A3, SLC6A4, IGF1R, GRM2, GRM5, STS, CA4, ADORA1, CA9, FFAR1, ACP1, KCNH2, ABCC1, DGAT1, SIGMAR1, AVPR2, AVPR1A, TACR1, OPRM1, BACE1, BACE2, AR, KIT, AGTR1, MET, UGT2B7, PTGES, ABCG2, CSF1R, ABCB1, MAOB, CHRNA7, PTGER3, OPRL1, HMGCR, CYP3A4, CYP19A1, EGFR, CRHR1, GLRA1, HSD11B2, EBP, CNR2, CNR1, CXCR3, HSD17B2, DRD2, DRD3, FDFT1, ST3GAL3, CA12, CCR1, PTPN1, BCHE, GABBR1, INSR, EPHX1, GPR55, ESR1, BCL2, DHCR7, PTPN2, GPR18, FGFR1, BCL2L1
GO:0019899	Enzyme binding	22	3.54E-12	TOP2A, PTPN1, BCHE, APP, SRC, PDE4D, PRKCD, PLG, CYP3A4, PTGS2, CYP2C19, HIF1A, ESR1, EGFR, ESR2, BACE1, AR, MDM2, AKT1, PGR, PPARG, MAPT
GO:0004712	Protein serine/threonine/tyrosine kinase activity	20	2.59E-09	PRKCG, ALK, CSF1R, PRKCB, SRC, INSR, PRKCD, DYRK1A, EGFR, IGF1R, CDK6, RPS6KB1, CDK4, KIT, CDK2, KDR, AKT1, MET, FGFR1, MAPK3
GO:0008270	Zinc ion binding	35	1.01E-14	NR1I3, RORA, NR3C1, NR3C2, GLRA1, SHH, CA1, CA5B, CA3, CA2, CA5A, CA4, CA7, CA6, CA9, CA13, SNCA, CA12, PRKCG, PTPN1, PRKCB, VDR, NR1H2, MMP2, NR1H3, MMP9, ESR1, SIRT2, ESR2, MMP12, AR, MDM2, PPARG, PGR, PPARD

We made a bubble chart out of the twenty most important KEGG pathway terms. The larger and more prominent bubbles show strongly enriched route terms. From the figure 4, we found that the metabolic pathways, pathways in cancer, and neuroactive ligand-receptor interactions were the enriched pathways.

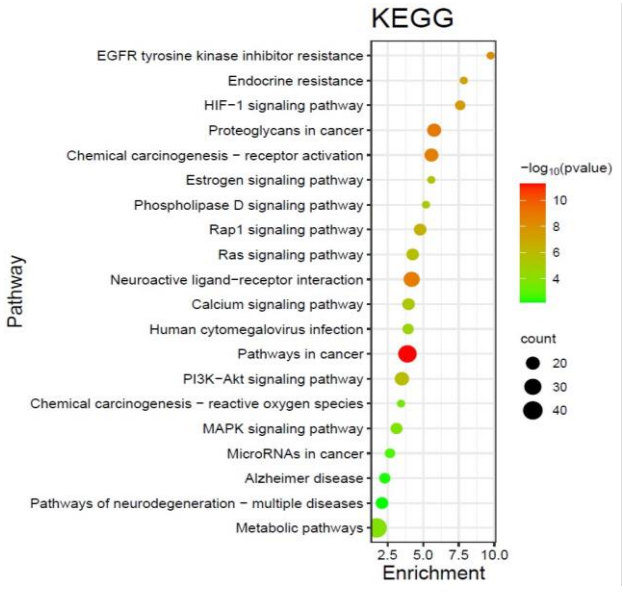


Figure (4): KEGG Pathway Enrichment Analysis of Essential Targets.

The image displays the primary results from GO enrichment analysis, which classifies the target genes according to their biological processes, molecular functions, and cellular components. The enrichment scores (-log10(p-value)) for the GO terms are plotted on the y-axis, representing the significance of their enrichment. The GO categories containing the target genes are shown in the x-axis (Biological Process, Molecular Function, and Cellular Component). This analysis demonstrates the functional roles of the identified target genes in epilepsy and their putative mechanisms of action.

The figure illustrates how the essential target genes are classified according to KEGG enrichment analysis. The x-axis corresponds to enrichment levels (-log10(p-value)), and the y-axis indicates the pathways involved. The size of the dot represents the number of enriched genes, and the intensity of color denotes statistical significance. This analysis emphasizes major biological pathways and potential therapeutic targets against epilepsy.

Upstream pathway

SPEED2 provides a simplified way for evaluating signalling activity for collections of malfunctioning genes found through transcriptomic data processing. Prioritising shared objectives helped us identify the source of the problem. Adjusted P-values were represented by colours, and absolute P-values were used to rank activities; higher-ranking colours indicated a greater influence from F. In addition, we examined which genes were frequently up-regulated or down-regulated after pathway disruption and found that the TNF-, TLR-, and IL-1 signalling

pathways were up-regulated, while the Hippo, PPAR pathway was down-regulated (when the adjusted P-value was greater than zero, the associated genes seemed up-regulated).

Countersignature of pathway activities through upstream pathway analysis filtered for statistical significance (adjusted p-value < 0.05) is depicted in the figure 5. The pathways were ranked according to their adjusted p-values, with the most significant pathways being represented at the top. The color gradient denotes adjusted p-values, with brighter colors representing higher significance (lower p-values). This visualization emphasizes the pathways pertinent to epilepsy, affording a prioritized repository for further exploration toward their therapeutic utility.

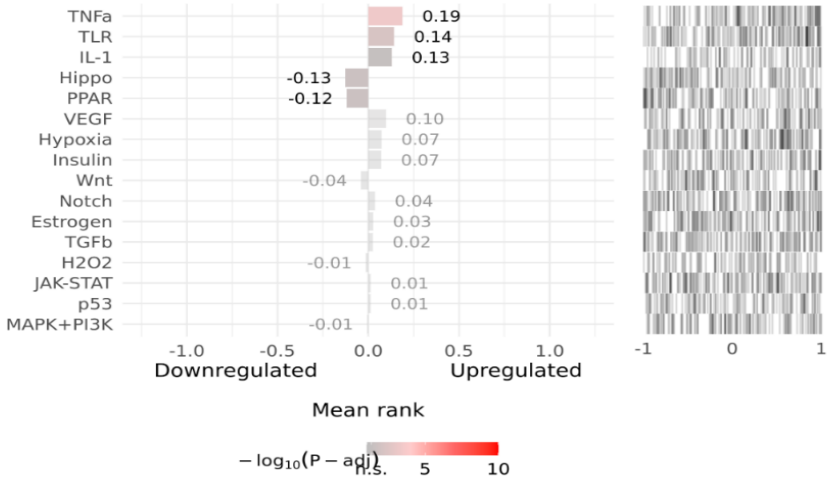


Figure (5): Ranking of Pathway Activities Based on Statistical Significance

Protein-Protein Interaction and Analysis of the Network

We identified 152 targets associated with CM and epilepsy. We imported the shared targets into STRING and then back into Cytoscape to build the PPI network. The string network has divided its scoring range into four segments: 0.150 for the lowest confidence score, 0.400 for medium confidence, 0.700 for strong confidence, and 0.900 for the maximum confidence.We found 152 nodes and 413 edges between them, with a clustering coefficient of 0.496 when we took into account a high scoring capacity (0.700). This figureshows the distinctive genes and their PPI connections. Multiple connected nodes in a PPI network may be labelled as hub genes at once. High-interaction proteins were discovered by analysing the network topology with the CytoHubba plugin. Using a “degree value” option, hub genes from the top 20 were filtered out [24, 25]. These include AKT1, TNF, SRC, ESR1, EGFR, PPARG, PTGS2, BCL2, HIF1A, MAPK3, MMP9, APP, CYP3A4, KDR, MDM2, IGF1R, PGR, NR3C1, HMGCR, and AGTR1 within the PPI network presented. The degree value of genes represents the overall number of edges within a network. Epilepsy genes that have a curative effect on plant CM were more likely to have a higher degree of significance.

The figure 6 represents a PPI network of potential target proteins involved in the molecular mechanism under investigation. Each node in the network represents a distinct protein, while the edges denote the predicted functional associations or interactions between these proteins. Nodes with a higher degree of connectivity signify hub proteins, which may play a crucial role in regulating the underlying biological process or disease pathology. The colors of the nodes indicate different functional categories or protein families, whereas the thickness of the edges represents the strength of the interaction. This network provides valuable insights into the molecular pathways and potential drug targets for therapeutic intervention

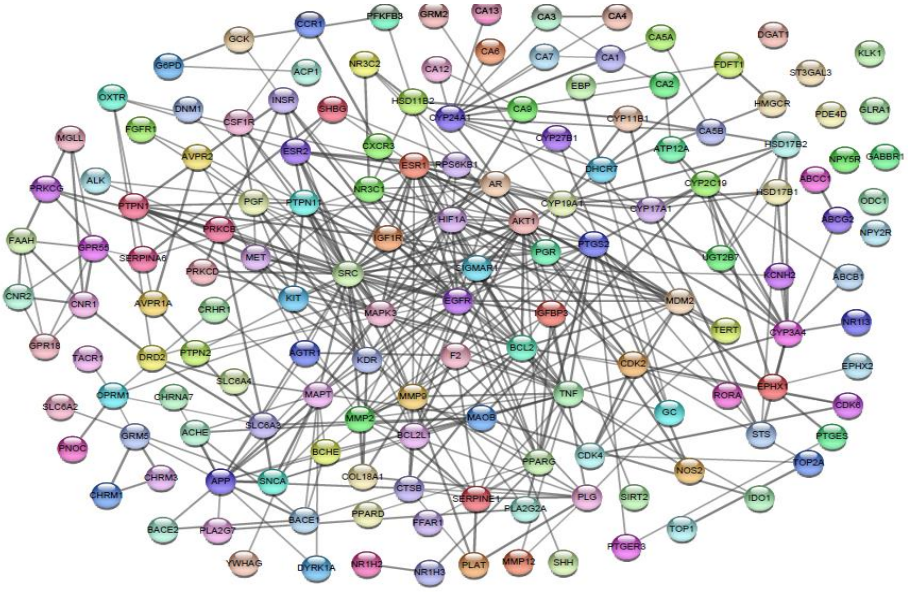


Figure (6): Protein-Protein Interaction (PPI) Network.

The figure 7 illustrates the integration of hub gene detection within the PPI network using the cytohubba plugin. A total of 20 hub proteins were identified based on the degree score approach, which measures the connectivity of each node (protein) within the network. The color gradient represents the degree scores, with redder colors indicating higher connectivity (more interactions) and yellower colors indicating lower connectivity (fewer interactions). This analysis highlights the most central and biologically significant proteins in the network, providing insights into their potential roles in epilepsy and guiding further experimental validation.

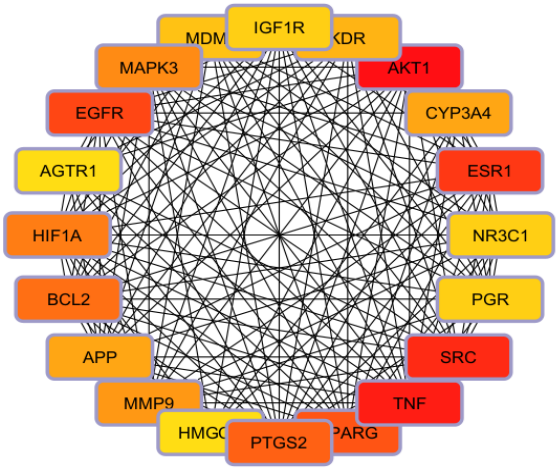


Figure (7): Identification of Hub Genes in the Protein-Protein Interaction (PPI) Network.

Network

The network was constructed, demonstrated, and analysed using Cytoscape version 3.10.0. It is based on how compounds interact with genes that overlap. The nodes in the network show the genes and compounds, while the edges depict the relationships between them.

The C-T network of CM and epilepsy developed with 11 candidate drugs associated with 152 possible targets. There was a total of 163 nodes (11 compounds, 152 targets) and 1671 edges in the effective compound-core target network, as depicted in figure 8. We built the T-P network by linking the 20 most important targets to the 20 most important KEGG pathways. Figure 9 depicts the target-pathway network, which consists of 40 nodes (20 targets, 20 paths), and 400 edges. The plant, the active ingredients of *Cucumis melo*, the top 20 targets (selected from cytohubba using the degree technique), and the top 20 KEGG pathways were used to construct the herb-compound-Target-Pathway network. which is composed of 52 nodes and 611 edges displayed in figure 10.

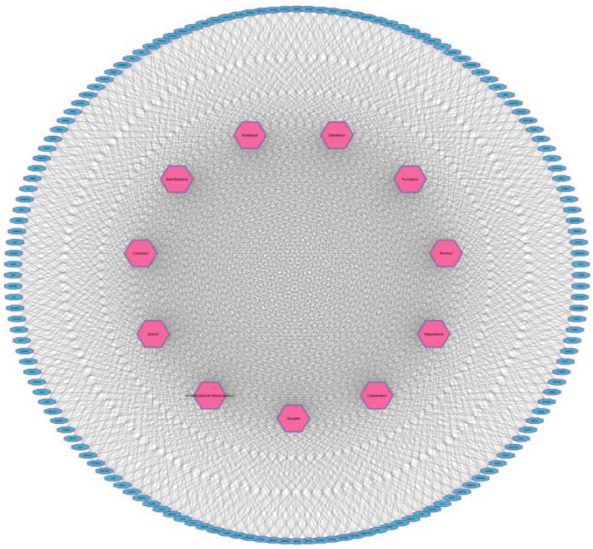


Figure (8): Network of Bioactive Compounds and Key Targets in *Cucumis melo* (CM) and Epilepsy

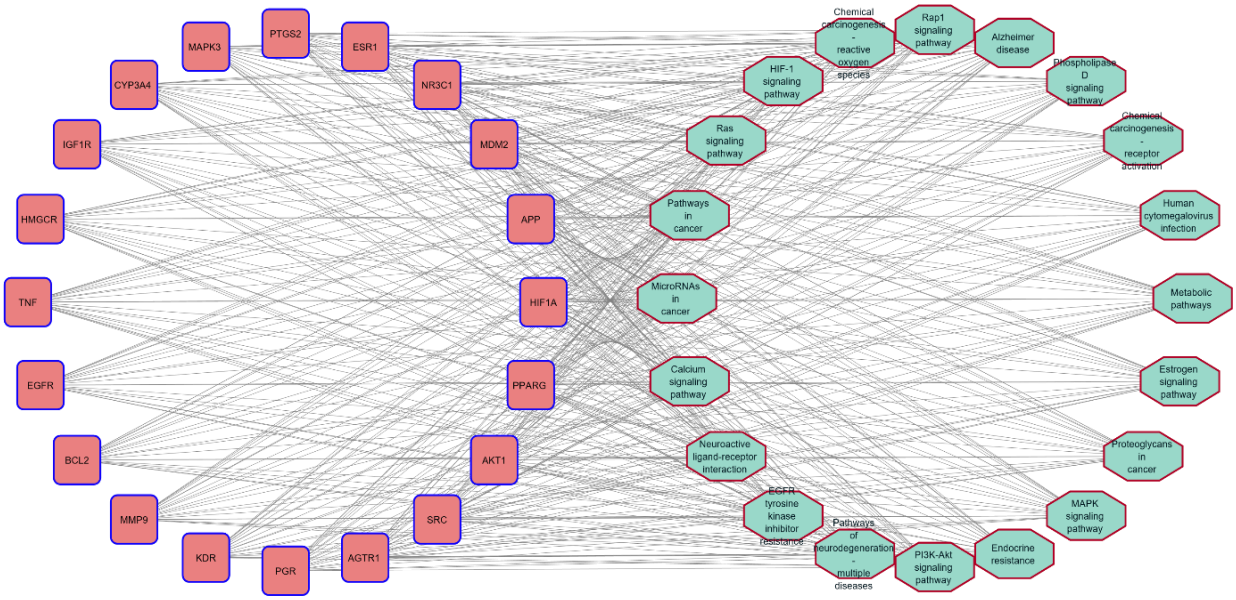


Figure (9): Target-Pathway Network.

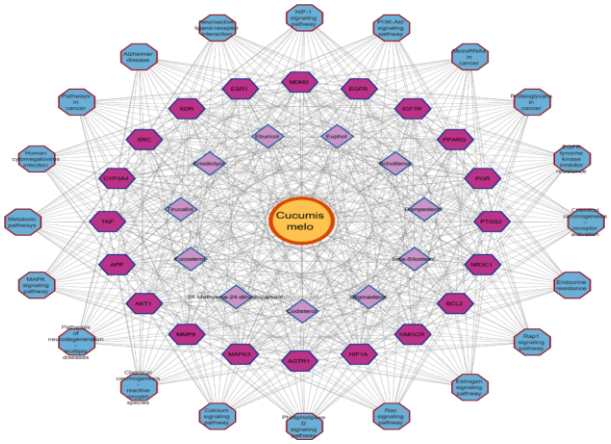


Figure (10): Herb-Compound-Target-Pathway Network.

This diagram portrays the interaction networks between CM bioactive compounds (pink hexagons) and key epilepsy-related target proteins (blue octagons) in the interaction network with grey edges suggested potential interactions. Pathways such as TNF-alpha signaling and metabolic regulation are of utmost importance. It is proposed that CM may reduce seizure susceptibility by reducing neuroinflammatory activity and restoring metabolic balance via bioactive compounds including cucurbitacins and flavonoids. Studies need to be carried out that validate these possible therapeutic uses.

In the figure, the target proteins (depicted as purple rhombuses) interact with pathways (represented by pink octagons) through grey edges that depict their associations. This network delineates important pathways modulated by CM's target proteins, thus providing sufficient insights into its proposed therapeutic mechanism for the treatment of epilepsy.

The integrated network of *Cucumis melo* (orange circles), bioactive compounds (purple rhombuses), target proteins (pink hexagons), and pathways (blue octagons) connected by grey edges depicts a multi-targeting multi-pathway therapy for epilepsies.

Molecular docking

The protein-ligand blind docking method works well for looking at both where receptors adhere and how ligands bind to them (Figure 11) [26]. It is suggested that molecular computational approaches predict the nature of a protein's interaction with ligands (Figure 12). Based on empirical data, Glide score provides a rough estimate of the free energy of ligand binding (Figure 13). To mimic binding free energy, it takes on increasingly negative values as the binding becomes more stable [27-32].

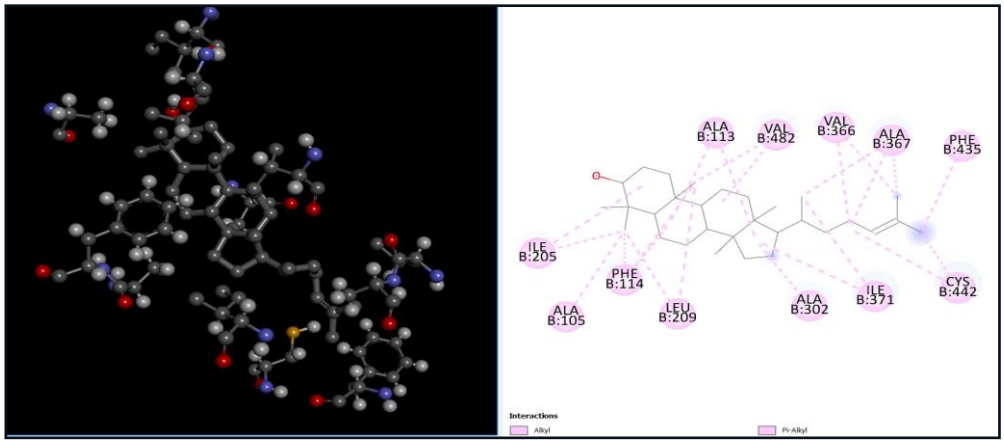


Figure (11): Eburicol – Dual specificity phosphatase.

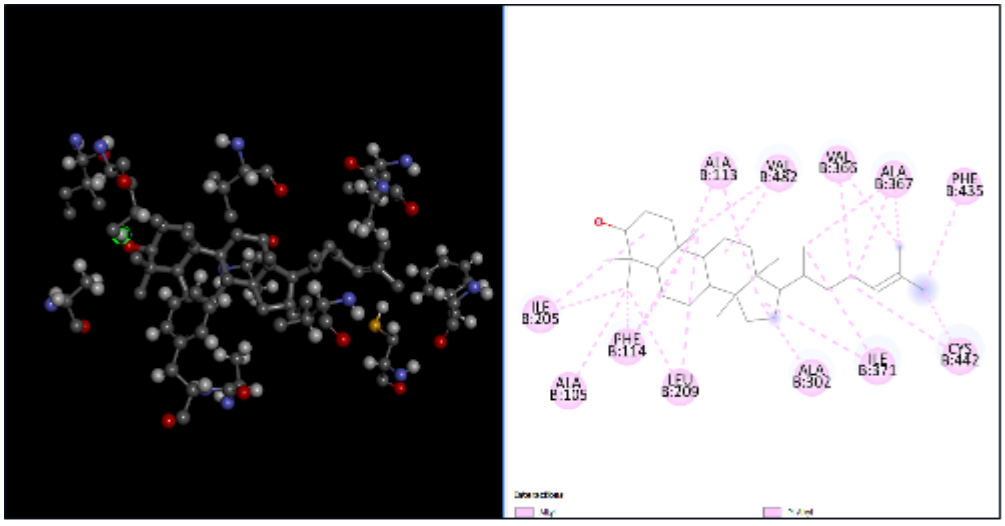


Figure (12): Euphol: Cytochrome P450 17A1.

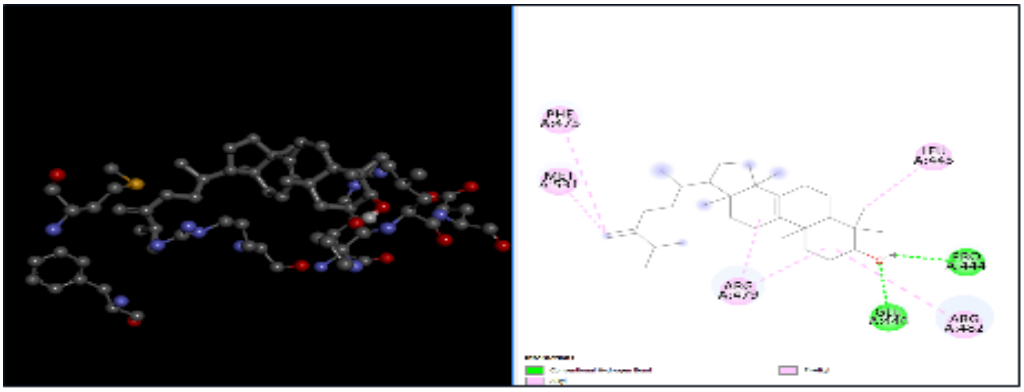


Figure (13): Triucallol - Cytochrome P450 17A1

There are potential biases from predictive algorithms and database limitations, such as incomplete data coverage or tool accuracy (e.g., CB-Dock2). Identified bioactives (e.g., eburicol) were compared to known antiepileptic drugs, showing overlapping mechanisms like GABA modulation. However, experimental validation is needed to confirm these findings and establish therapeutic relevance.

Conclusion

We researched the components and mechanisms of possible anticonvulsive activity in *Cucumis melo* by network pharmacology and molecular docking. The study revealed 11 bioactive compounds and 152 target genes linked to CM's effects against epilepsy. Based on binding energy values, eburicol emerged as the potent active compound, while AKT1 was considered a major hub protein. The majority of significant pathways included metabolic process, response to xenobiotic stimulus, and TNF-alpha signaling pathways, emphasizing CM's promising multi-target potential. Upon protein-protein interaction analysis, 20 hub genes with strong interactions to CM compounds substantiated their involvement in epilepsy modulation.

Although they provide preliminary but desired insights into CM capability for therapy, experimental validation is essential as they are at present based on computational prediction. The next

step should include *in vitro* and *in vivo* testing to check efficacy using compounds of interest, such as eburicol, and understanding the mechanisms involved. Moreover, formulation development as well as preclinical studies are important in advancing CM to clinical applicability. Despite laying a foundation for further study, this work calls for stringent experimental validation to make these findings practical treatments for epilepsy.

Disclosure Statements

- **Ethics approval and consent to participate:** Not Applicable
- **Consent for publication:** Not Applicable
- **Availability of data and materials:** The data is obtained from various databases like IMPPAT, SMILES, GENE cards, OMIM, STRING, CYTOSCAPE.
- **Author's contribution:** Suvarchala Reddy, M. Ganga Raju, Keerthana Edunoori, M. Mamatha, M. Lakshmi Madhuri, Shabnam Kumari Thakur & Nisha Shri conceived and planned the experiments. Keerthana Edunoori, M. Mamatha, M. Lakshmi Madhuri & Shabnam Kumari Thakur carried out the experiments. Keerthana Edunoori, M. Mamatha, Shabnam Kumari. and Suvarchala Reddy contributed to the interpretation of the results. Suvarchala Reddy, M. Ganga Raju, Keerthana Edunoori took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.
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