

Predictive Data Modeling of C1SD2 Activation for Neuroprotection: Insights from In Silico and Machine Learning Approaches

Introduction & Background

- C1SD2 maintains mitochondrial and endoplasmic reticulum (ER) functions, regulating oxidative phosphorylation, redox balance, and calcium homeostasis.
- Reduced C1SD2 expression exacerbates neurodegeneration in Parkinson's and Alzheimer's diseases.
- Neurodegenerative diseases currently lack effective treatments; C1SD2 dysfunction contributes to mitochondrial malfunction, oxidative stress, and neuronal death.
- The hypothesis is that enhancing C1SD2 expression via small-molecule activators like Liquiritigenin could reduce oxidative stress, maintain mitochondrial integrity, and prevent neuronal death.

Methods

- An integrated computational approach was used, including UCSC Genome Browser for gene sequence retrieval, BLAST X for mutation analysis, PSI-PRED for secondary structure prediction, Swiss-Model for 3D modeling, and Autodock Vina for molecular docking.
- C1SD2 nucleotide sequence was retrieved from genomic databases; protein mutations (T28V, T28L, T28S, P24L) were analyzed via multiple bioinformatics tools for pathogenicity and stability.
- Secondary and tertiary protein structures were predicted and validated using PSI-PRED, Swiss-Model, ERRAT (96.552 overall quality factor), and Ramachandran plots.
- Molecular docking of Liquiritigenin to C1SD2 was performed with Autodock Vina (-6.2 kcal/mol binding affinity); pharmacological target prediction and ADMET analyses assessed drug-like properties.

Results

Gene Sequence and Mutation Analysis

- C1SD2 nucleotide sequence successfully extracted from UCSC Genome Browser and used for mutation detection and protein translation.
- Four mutations identified (T28V, T28L, T28S, P24L); all classified as benign with PolyPhen-2. Most mutations predicted to decrease protein stability except T28S and P24L.

Protein Structural Modeling

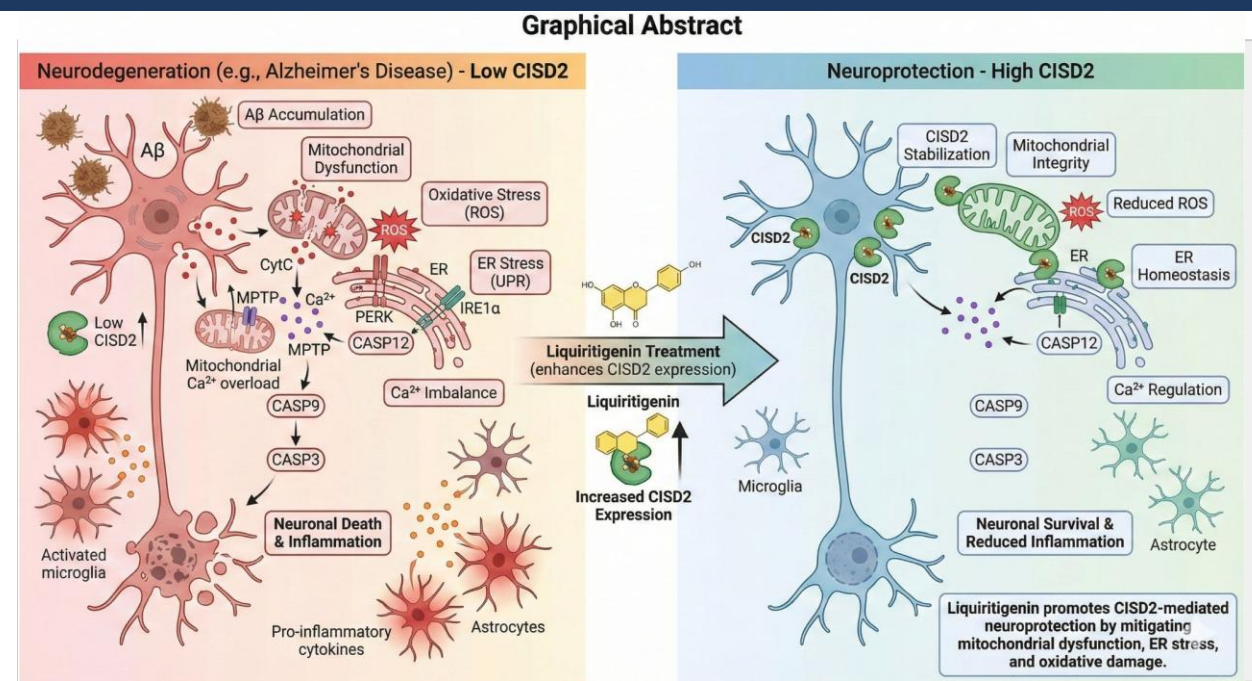
- PSI-PRED predicted protein secondary structure featuring helical and coiled regions, highlighting small nonpolar, hydrophobic, polar, and aromatic amino acid distributions with confidence scores.
- Swiss-Model generated a reliable 3D C1SD2 structure characterized by alpha-helices and loops; validation by ERRAT yielded an overall quality factor of 96.552.

Molecular Docking and Pharmacological Analysis

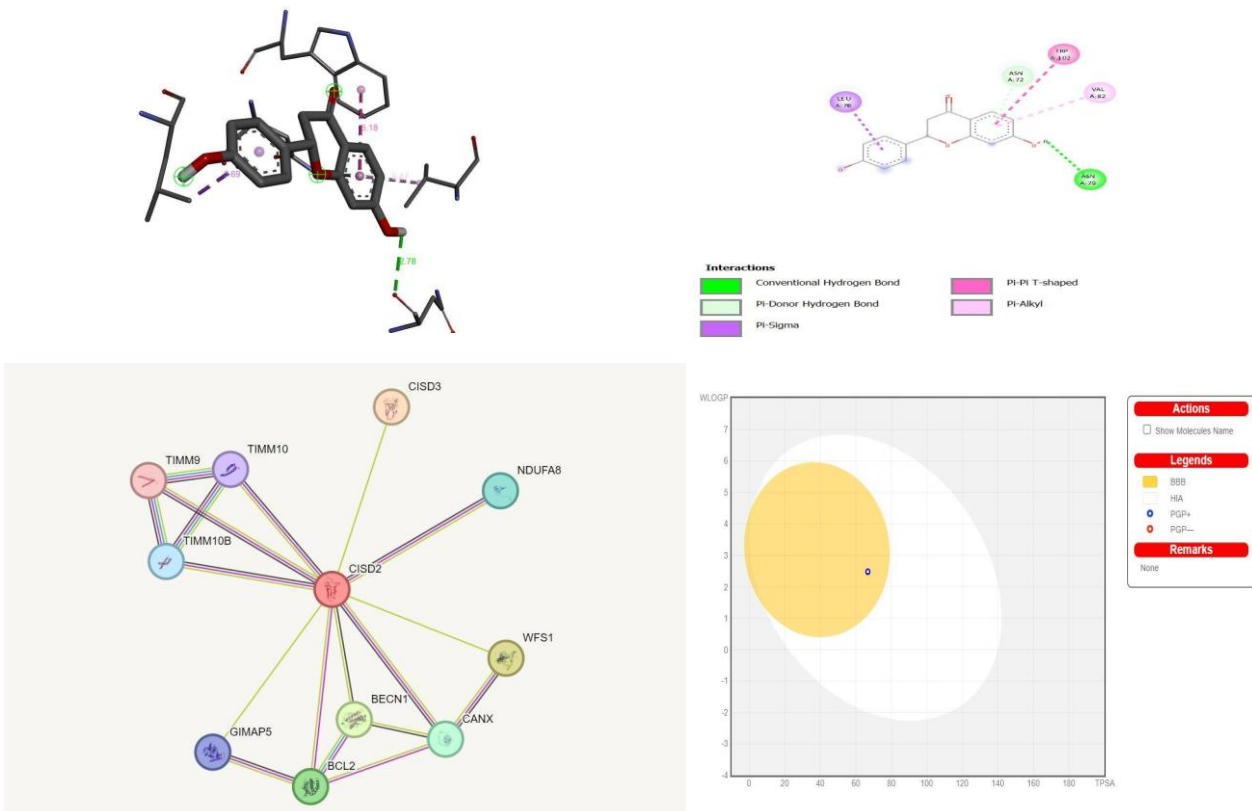
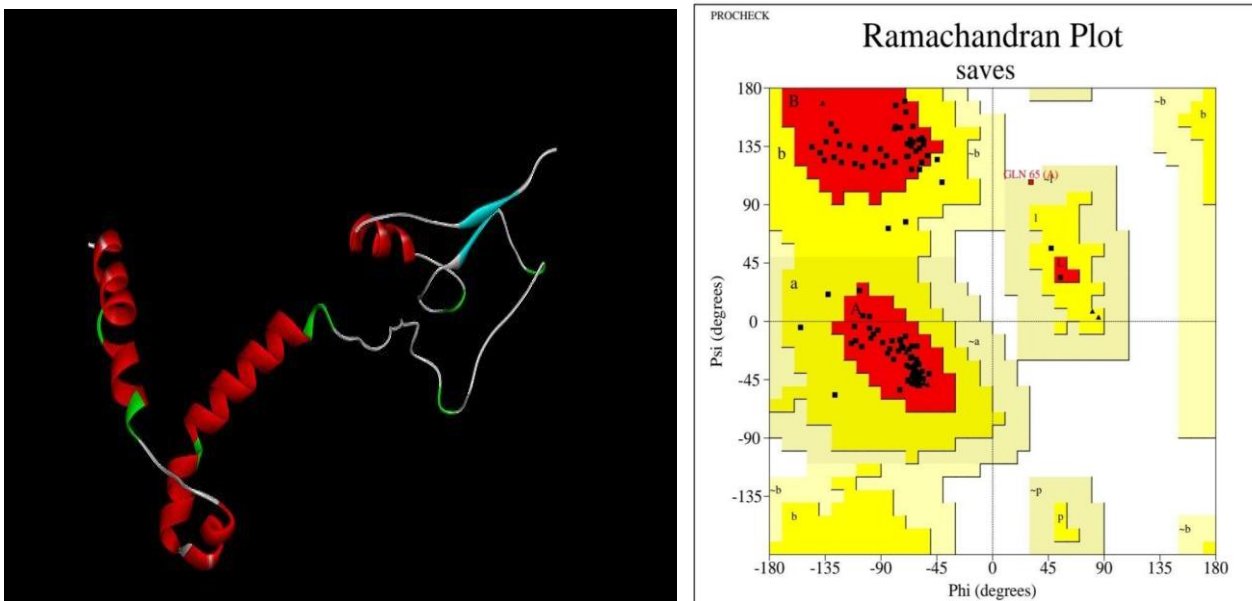
- Liquiritigenin exhibited a binding affinity of -6.2 kcal/mol to C1SD2's 3D structure, forming multiple hydrogen bonds including conventional H-bonds, pi-donor H-bonds, and pi-sigma interactions.
- Swiss Target Prediction identified various pharmacological targets including cytochrome P450, enzymes, primary amine oxidase, nuclear receptor, and secreted proteins.
- ADMET evaluation indicated Liquiritigenin has high gastrointestinal absorption, complies with Lipinski's rule, and displays favorable physicochemical and pharmacokinetic properties for drug development.

Key Findings

- C1SD2 protein was successfully modeled in 3D with high quality, enabling reliable molecular docking.
- Liquiritigenin demonstrated a strong binding affinity (-6.2 kcal/mol) and multiple hydrogen bonding interactions with C1SD2, confirming activation potential.
- ADMET analysis revealed high gastrointestinal absorption and Lipinski rule compliance indicating favorable drug-like properties.
- These computational findings support Liquiritigenin as a promising small-molecule activator of C1SD2 for neuroprotection.



Visual representation of the research concept and main finding



Discussion & Implications

- Activation of C1SD2 by Liquiritigenin may reduce oxidative stress, maintain mitochondrial integrity, and consequently prevent neuronal death in neurodegenerative disorders.
- C1SD2 is an essential regulator of mitochondrial function and ER stress response; its activation represents a promising therapeutic avenue for Parkinson's and Alzheimer's diseases.
- Computational docking and pathway analyses provide mechanistic insights supporting the neuroprotective role of Liquiritigenin-mediated C1SD2 activation.
- This study is limited to computational analyses lacking in vitro and in vivo validation; biological studies are essential to confirm efficacy and safety.
- Future work should include cellular and animal models to validate C1SD2 activation timing in disease progression and explore additional CDGSH modulating compounds.