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REVIEWER'S REPORT

Manuscript No.: JNHM-057

Title: Network Pharmacology study of antiepileptic active agents

Recommendation:

Accept as it is .....YES.....

Accept after minor revision.....

Accept after major revision .....

Do not accept (*Reasons below*) .....

Rating	Excel.	Good	Fair	Poor
Originality		√		
Techn. Quality		√		
Clarity		√		
Significance		√		

Reviewer Name: PROF. DR DILLIP KUMAR MOHAPATRA

Detailed Reviewer's Report

The manuscript titled **"Network Pharmacology Study of Antiepileptic Active Agents"**.

1. Strengths of the Study

Relevant and timely topic: The study addresses epilepsy, a complex neurological disorder requiring multi-target therapeutic strategies, making network pharmacology an appropriate and modern approach.

Rational methodological framework: Integration of target prediction, disease target screening, compound–target–disease network construction, PPI analysis, and GO/KEGG enrichment provides a systematic and holistic investigation.

Focus on hydantoin derivatives: Hydantoins are a clinically validated scaffold (e.g., phenytoin), and exploring their multi-target mechanisms adds novelty and pharmacological relevance.

Compound-wise network analysis: Evaluation of individual compounds (1–10) using topological parameters (degree, betweenness, closeness) strengthens lead identification.

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Identification of key targets: Highlighting mGluR5 and related glutamatergic signaling pathways is biologically plausible and well supported by existing epilepsy literature.

Clear lead prioritization: Compounds 4, 6, and 10 are logically identified as promising leads based on network influence.

2. Weaknesses of the Study

Lack of experimental validation: The study relies entirely on in-silico predictions; no in vitro, in vivo, or clinical validation is provided to confirm biological relevance.

Limited justification for protein selection: The exclusive focus on mGluR5 (PDB ID: 5KZQ) could be better justified, given that epilepsy involves multiple ion channels and receptors.

Redundancy in references: Some references are repeated or overlap in content, reducing citation diversity.

Insufficient discussion on limitations: The manuscript does not adequately discuss inherent limitations of network pharmacology tools, such as database bias and prediction uncertainty.

Bioavailability uniformity: Reporting identical bioavailability values (0.55) for all compounds may raise concerns regarding prediction realism and needs clarification.

Language and formatting issues: Minor grammatical errors, repetition, and formatting inconsistencies are present and require editorial polishing.

3. Significance of the Study

The study **enhances mechanistic understanding** of hydantoin derivatives beyond traditional single-target sodium channel modulation.

It **supports the concept of polypharmacology** in epilepsy treatment, aligning with modern drug discovery paradigms.

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Identification of **glutamatergic signaling and mGluR5 as central hubs** provides valuable insights for future antiepileptic drug design.

The work offers a **computational screening framework** that can reduce time and cost in early-stage antiepileptic drug discovery.

The findings have translational potential by guiding **molecular docking, molecular dynamics, and experimental studies**.

4. Key Points of the Manuscript

Network pharmacology was applied to explore the **multi-target antiepileptic mechanisms** of hydantoin derivatives.

Target prediction and disease gene screening identified **shared epilepsy-associated targets**.

Compound–target–disease and PPI networks revealed **key hub genes**, particularly metabotropic glutamate receptors (GRM family).

GO and KEGG enrichment analyses highlighted pathways related to **glutamate signaling, calcium regulation, synaptic transmission, and neuronal excitability**.

Compounds 4, 6, and 10 emerged as top lead candidates based on network topology.

The study provides a **computational foundation** for further docking, dynamics simulations, and experimental validation.