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Peer Review

Review of: "New Approach for TargetingSmall Molecule Candidates for Intrinsically Disordered Proteins"

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The study under review tackles a critical and complex challenge in neurodegenerative disease research: the discovery of therapeutic modulators for intrinsically disordered proteins (IDPs), with a particular focus on the tau protein, a hallmark of Alzheimer's disease pathology. IDPs present unique difficulties for conventional structure-based drug design due to their lack of stable tertiary structure. In this context, the authors propose the Informational Spectrum Method for Small Molecules (ISM-SM) as a computational tool that leverages electron-ion interaction potentials (EIIP) to identify small molecules capable of modulating tau function. This innovative approach is both timely and promising, offering a potentially valuable strategy for addressing an area of drug discovery where few viable solutions exist.

One of the study's strengths lies in its clear articulation of ISM-SM's ability to bypass structural constraints by focusing on informational frequencies derived from both conserved tau sequences and known ligands. This spectral approach represents a compelling alternative to traditional docking or molecular dynamics methods, particularly for IDPs. The use of conserved sequence motifs across mammalian tau proteins suggests that the authors aimed for broad biological relevance, which is commendable. However, the manuscript could benefit from a more detailed description of how the identified frequencies were selected and validated as "characteristic" for tau modulators. Greater transparency in this step would strengthen confidence in the method's specificity and reproducibility.

The study's application of ISM-SM to screen the DrugBank and COCONUT databases adds practical value by incorporating both approved pharmaceutical compounds and diverse natural products. Notably, several known modulators of tau-related pathways—such as Bryostatin-14—were among the hits, supporting the method's validity. This dual screening strategy broadens the potential utility of the findings, aligning well with current trends in drug repurposing and the exploration of bioactive natural

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compounds. Nonetheless, the study does not clearly report the total number of compounds screened, the selection thresholds applied, or how statistical significance was determined for candidate hits. Including such methodological details would improve the interpretability and utility of the results for other researchers.

An encouraging aspect of the findings is the identification of both known and novel compounds associated with Alzheimer's disease or tau phosphorylation pathways. This overlap with existing literature adds credibility to the ISM-SM technique. However, a more thorough discussion of the functional relevance of each identified compound—particularly those not previously linked to tau—would be beneficial. Are these compounds predicted to act through direct interaction with tau, or via modulation of upstream kinases and signaling cascades? Such clarification would enhance the biological interpretability of the computational results.

Another important consideration is the lack of experimental validation or follow-up analysis to confirm the predicted interactions. While the in silico approach provides a rapid and cost-effective screening method, its translational relevance remains speculative in the absence of empirical data. Including docking simulations, biophysical assays, or cellular models in future studies would significantly enhance the robustness of the conclusions. Furthermore, it would be valuable to know whether the ISM-SM method can distinguish between agonists, antagonists, or allosteric modulators in this context.

In terms of presentation, the manuscript is clearly written and generally well-structured, although the addition of a workflow diagram or visual summary of the ISM-SM process would greatly improve clarity, especially for readers unfamiliar with spectral methods. Similarly, a tabulated summary of the top hits, along with their known biological activities, would aid comprehension and facilitate future research efforts. Providing these elements would make the paper more accessible to interdisciplinary audiences, including biologists and pharmacologists who may not be deeply versed in computational screening techniques.

A particularly compelling strength of this work is its potential complementarity with existing drug discovery strategies. As IDPs like tau remain difficult to target with traditional structure-based techniques, ISM-SM may fill a critical methodological gap. The authors briefly acknowledge this synergy but could expand further on how ISM-SM might be integrated into multi-step pipelines involving target validation, functional screening, and in vivo efficacy studies. Doing so would increase the method's perceived practical relevance to translational research.

Despite the promising results, the study also raises several unanswered questions. For example, how sensitive is ISM-SM to sequence variations in tau isoforms? Could this method be applied to tau aggregates or post-translationally modified forms of the protein, which are more pathologically relevant? Moreover, the manuscript does not discuss potential limitations related to off-target predictions or false positives—a common challenge in computational screening. A critical evaluation of such caveats would strengthen the study's scientific rigor and trustworthiness.

The authors conclude by proposing ISM-SM as a useful tool for identifying tau-targeting compounds, especially in the context of IDP-related drug discovery. This is a well-founded assertion, and the study lays a strong conceptual and methodological foundation for future work. Nevertheless, the utility of ISM-SM would be greatly enhanced by coupling its predictions with experimental validation and expanding its application to a broader array of IDP targets. Such efforts could eventually lead to the identification of novel therapeutics for Alzheimer's disease and other neurodegenerative conditions.

In summary, this study presents a creative and potentially impactful computational strategy for identifying modulators of the tau protein through the Informational Spectrum Method. Its integration of approved drugs and natural products offers both practicality and innovation. While the study excels in methodological originality and biological relevance, it would benefit from greater methodological transparency, deeper biological analysis of the hits, and some form of experimental corroboration. Nevertheless, it contributes meaningfully to the evolving landscape of IDP-targeted drug discovery and opens promising avenues for further research and development.

Declarations

Potential competing interests: No potential competing interests to declare.