Editor-in-Chief
Computational Toxicology
Elsevier

Antony Bevan
Department of Pharmacognosy
Madurai Medical College
Madurai 625020, India
Email: antonybevan04@gmail.com

January 21, 2026

To the Editor-in-Chief
Computational Toxicology
Elsevier Editorial Office

Subject: Submission of Original Research Article

Dear Editor,

I am pleased to submit our manuscript, "**Comparative analysis of network-based measures for the assessment of drug-induced liver injury: A case study of *Hypericum perforatum***," for consideration as an Original Research Article in *Computational Toxicology*.

In this study, we address a critical methodological vulnerability in network-based toxicology: the sensitivity of proximity Z-scores to target-set size. Using *H. perforatum* as a model, we demonstrate that traditional proximity-based rankings are fundamentally confounded by the law of large numbers, which leads to unstable, threshold-dependent significance assessments when comparing compounds with asymmetric target profiles.

To resolve this, we provide a robust framework based on random walk influence propagation and introduce **Per-Target Network Influence (PTNI)** as a normalized metric for perturbation efficiency. Our results show that influence-based metrics remain stable across network construction parameters and correctly identify the high-leverage modulation of the PXR axis by hyperforin, where proximity measures fail.

We believe this work is particularly relevant to the readers of *Computational Toxicology* as it identifies a systematic artifact in current prioritization workflows and provides a validated, reproducible alternative for comparative risk assessment.

This manuscript is original and is not under consideration elsewhere. All code and curated data have been made available via a public repository (https://github.com/antonybevan/h-perforatum-network-tox) to ensure complete transparency and reproducibility.

Thank you for your time and for considering our work.

Sincerely,

Antony Bevan