ABSTRAK

Pendahuluan: Penurunan fungsi kognitif berkaitan dengan gangguan neurotransmisi kolinergik sehingga asetilkolinesterase (AChE) menjadi target yang relevan. *Bacopa monnieri* secara tradisional digunakan untuk mendukung fungsi kognitif, tetapi metabolit yang berkontribusi terhadap potensinya belum sepenuhnya dikarakterisasi.
Metode: Penelitian ini mengintegrasikan profil metabolit tidak tertarget menggunakan *liquid chromatography–high-resolution mass spectrometry* (LC–HRMS), *molecular docking*, simulasi dinamika molekuler 10 ns, evaluasi *drug-likeness* berdasarkan aturan Lipinski, dan prediksi toksisitas oral akut. Data LC–HRMS diproses menggunakan Compound Discoverer 3.2. Delapan metabolit dievaluasi terhadap AChE menggunakan DockThor-VS, sedangkan baicalin, luteolin-7-*O*-glucuronide, maslinic acid, dan kaempferol dilanjutkan ke simulasi dinamika molekuler dengan donepezil sebagai pembanding.
Hasil: LC–HRMS menghasilkan 100 fitur metabolit; 64 memperoleh anotasi putatif dan 47 metabolit unik dipertahankan setelah kurasi. Sebanyak 20 metabolit diprioritaskan. Baicalin memperoleh DockTScore paling negatif sebesar −10,456. Pada simulasi dinamika molekuler, kompleks AChE–kaempferol menunjukkan RMSD backbone sebesar 0,1147 ± 0,0108 nm, relatif mendekati AChE–donepezil sebesar 0,1099 ± 0,0101 nm, serta menunjukkan RMSD ligan yang lebih rendah dibandingkan donepezil. Luteolin-7-*O*-glucuronide menunjukkan RMSD backbone dan ligan terendah di antara kandidat yang disimulasikan. Kaempferol tidak menunjukkan pelanggaran aturan Lipinski dan diprediksi berada pada kelas toksisitas oral akut V.
Kesimpulan: Integrasi hasil *molecular docking*, simulasi dinamika molekuler, *drug-likeness*, dan prediksi toksisitas menunjukkan bahwa kaempferol memiliki profil komputasional yang paling seimbang dan diprioritaskan sebagai kandidat utama untuk validasi eksperimental lebih lanjut. Hasil penelitian ini masih bersifat prediktif dan belum membuktikan aktivitas penghambatan AChE maupun efek nootropik kaempferol secara eksperimental.

Kata kunci: *Bacopa monnieri*; kaempferol; asetilkolinesterase; LC–HRMS; *molecular docking*; dinamika molekuler; *drug-likeness*.

ABSTRACT

Introduction: *Cognitive decline is associated with impaired cholinergic neurotransmission, making acetylcholinesterase (AChE) a relevant molecular target. Bacopa monnieri has traditionally been used to support cognitive function; however, the metabolites contributing to its potential effects have not been fully characterized.*

Methods: *This study integrated untargeted metabolite profiling using liquid chromatography–high-resolution mass spectrometry (LC–HRMS), molecular docking, 10-ns molecular dynamics simulations, Lipinski-based drug-likeness evaluation, and acute oral toxicity prediction. LC–HRMS data were processed using Compound Discoverer 3.2. Eight metabolites were evaluated against AChE using DockThor-VS, while baicalin, luteolin-7-O-glucuronide, maslinic acid, and kaempferol were further subjected to molecular dynamics simulations, with donepezil used as the reference compound.*

Results: *LC–HRMS analysis generated 100 metabolite features; 64 received putative annotations, and 47 unique metabolites were retained after curation. Twenty metabolites were prioritized. Baicalin showed the most negative DockTScore at −10.456. In molecular dynamics simulations, the AChE–kaempferol complex showed a backbone RMSD of 0.1147 ± 0.0108 nm, relatively close to that of AChE–donepezil at 0.1099 ± 0.0101 nm, while its ligand RMSD was lower than that of donepezil. Luteolin-7-O-glucuronide showed the lowest backbone and ligand RMSD values among the simulated candidates. Kaempferol showed no Lipinski rule violations and was predicted to belong to acute oral toxicity class V.*

Conclusion: *Integration of molecular docking, molecular dynamics simulation, drug-likeness, and toxicity prediction indicated that kaempferol exhibited the most balanced computational profile and was prioritized as the main candidate for further experimental validation. These findings remain predictive and do not establish experimental AChE inhibition or nootropic activity of kaempferol.*

Keywords: *Bacopa monnieri; kaempferol; acetylcholinesterase; LC–HRMS; molecular docking; molecular dynamics; drug-likeness.*