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Novel curcumin derivatives loaded chitosan nanoparticles as therapeutic agents for alzheimer's disease: an *in-silico* evaluation

Fernando A. K. M.[2] and Dahanayake J. N.[1*]

[1] *Department of Chemistry, University of Kelaniya, Sri Lanka*

[2] *College of Chemical Sciences, Institute of Chemistry Ceylon, Rajagiriya 10107, Sri Lanka.*

**jayangikadh@kln.ac.lk*

Alzheimer's disease is an irreversible neurodegenerative disorder defined by signs and symptoms that include β-amyloid plaques, tau neurofibrillary tangles, and synaptic dysfunction. Treatments currently available are only palliative, but curcumin has shown promise in the treatment of Alzheimer's disease due to its neuroprotective and anti-inflammatory properties; however, curcumin is limited by low solubility and bioavailability. This study was designed to evaluate novel curcumin derivatives enclosed within chitosan nanoparticles for improved delivery, blood-brain barrier penetration, and therapeutic potential against AD. Six derivatives—bisdemethoxycurcumin, curcumin pyrimidine hybrid, quinolone hybrid, imidazole hybrid, thalidomide hybrid, and di-indole hybrid—were selected, their geometries optimized with DFT using Gaussian software, and subjected to molecular docking against key AD-specific proteins: amyloid precursor protein, acetylcholinesterase (AChE), tau protein, amyloid β-a, and amyloid β-a fibrils. Native curcumin and the FDA-approved drug donepezil were used as references. The quinolone hybrid showed the strongest binding to AChE (-9.63 kcal/mol), followed by thalidomide (-9.29 kcal/mol) and di-indole (-9.26 kcal/mol), outperforming curcumin (-7.43 kcal/mol) and approaching donepezil (-10.51 kcal/mol). These three compounds also demonstrated favorable interactions with other AD targets, suggesting multitarget potential. To enhance delivery, a chitosan nanoparticle system was evaluated and energy-minimized to simulate a spherical nanocarrier structure. Docking of the nanocarrier with the top three derivatives revealed favorable binding energies of -6.28 kcal/mol (quinolone), -7.37 kcal/mol (thalidomide), and -6.73 kcal/mol (di-indole), confirming good encapsulation. ADMET and toxicity predictions using ADMETlab 2.0 indicated the quinolone hybrid had the most favorable safety profile, while the others remained within acceptable limits. Overall, the quinolone, thalidomide, and di-indole hybrids are promising anti-Alzheimer agents, with the quinolone derivative showing the best efficacy-safety profile. Molecular dynamics simulation of the quinolone hybrid–AChE complex, conducted over 50 ns, demonstrated stable binding interactions, further validating its potential as a lead candidate.

Keywords:
Acetylcholinesterase; Alzheimer's disease; chitosan nanoparticles; curcumin derivatives; molecular docking