Abstract No: 2025_311

Altering bioavailability in curcumin derivatives- an *in silico* study

Lakna W. P. D.[1], Mohomed A.[2], and Keerthi A. P. P.[1]*

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

[2] *Eurofins Biopharma, United States.*

* *aapkeerthi1976@yahoo.com*

Curcumin and its derivatives exhibit diverse pharmacological activities, including antioxidant, anti-inflammatory, anti-proliferative, antibacterial, analgesic, and antiviral effects. However, their therapeutic potential is often limited by poor bioavailability, primarily due to low intestinal absorption. In this *in silico* study, we screened 198 curcumin derivatives identified in previous studies for toxicological profiles, bioavailability, and drug-likeness. Structural similarities among the derivatives were analyzed using Tanimoto similarity indices to identify key structural features influencing pharmacokinetic properties. This structural analysis was used to identify trends that could be attributed to receptor binding and guide the development of novel curcumin derivatives with improved drug-like properties. The top-ranked molecules from the screening were geometry optimized *via* Gaussian with a basis set of 6-311G++dp using the B3LYP hybrid density functional theory. The resulting molecules were then subjected to molecular docking (using Autodock Vina) against the human intestinal oligopeptide transporter 1 (PepT1), a known active transporter involved in drug absorption. Among the tested derivatives, the molecule designated as "C09" exhibited the highest docking score of -8.5 kcal mol^{-1}, suggesting strong binding affinity to PepT1. To further enhance bioavailability, the same set of curcumin derivatives was conjugated with a dipeptide and reassessed for binding interactions with PepT1. The results indicated that dipeptide-conjugated curcumin derivatives consistently displayed higher docking scores compared to their non-conjugated counterparts. The enhanced binding affinities of dipeptide-conjugated derivatives were attributed to additional stabilizing interactions with key residues in the PepT1 binding pocket, including LYS140, ARG27, ASN171, TYR31, GLU595, and TRP294. These findings suggest that dipeptide conjugation enhances the interactions of curcumin derivative with PepT1, potentially improving absorption and bioavailability. This study provides a rational basis for designing bioavailable curcumin derivatives and highlights the role of structural similarity analysis in optimizing drug candidates.

Keywords:
Curcumin derivatives; drug-likeness, intestinal absorption; PepT1; molecular docking