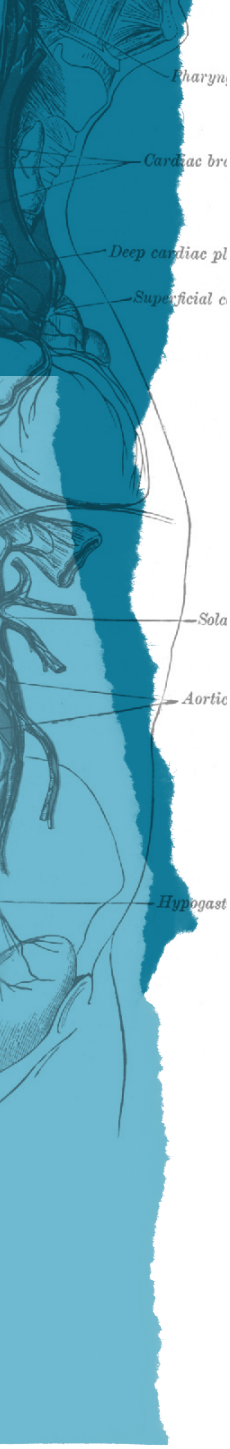

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In Silico Evaluation of Natural Compounds as Inhibitors of the Oropouche Virus Gc Glycoprotein

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ABSTRACT

Introduction: Oropouche virus (OROV) is an emerging orthobunyavirus in the Americas with no approved antiviral therapies.

Methods: This work employed a structure-based *in-silico* pipeline to identify natural compounds with potential to inhibit the Gc glycoprotein, a class II fusion protein essential for viral entry.

Results: A curated library of 537 phytochemicals was filtered by structural similarity, selecting 20 top candidates (flavonoids and alkaloids). Molecular docking against the Gc "head" domain (PDB: 6H3X) was followed by 100-nanosecond molecular dynamics simulations in YASARA, MM-PBSA binding free energy estimations, and ADMET profiling. Quercetin, previously reported as a putative OROV inhibitor, served as the reference ligand in all dynamic analyses. Significantly, curcumin and berberine demonstrated outstanding performance, combining favorable binding energies (–38.14 and –13.10 kcal/mol, respectively) with high structural stability (RMSD ≤ 1.82 Å) throughout the simulations. Curcumin additionally exhibited a highly favorable pharmacokinetic profile, whereas berberine's potent interaction was tempered by predicted cytotoxicity and mutagenicity signals, suggesting the need for structural optimization. Cynaroside, baicalin, and naringin also maintained stable interactions, although their predicted low oral bioavailability may limit direct clinical translation. It is notable that in this model, more positive or near-zero binding energy values were interpreted as indicative of more favorable ligand-protein interactions, a criterion consistent with the evaluation algorithms implemented in YASARA, which integrates molecular mechanics with empirical force field optimizations for high-precision affinity estimation. The use of YASARA was strategic due to its robust energy minimization protocols, solvent-aware dynamics, and reproducibility over extended simulation times.

Conclusions: Collectively, these findings position curcumin and berberine as highly promising molecular scaffolds for the rational development of novel antivirals against OROV, with translational potential to other emerging orthobunyaviruses. Ultimately, their performance in silico underscores the urgent need for experimental validation and paves the way for targeted antiviral discovery pipelines, a critical step in strengthening preparedness against arboviral threats in Latin America.

Keywords: Oropouche virus, Gc glycoprotein, natural compounds, molecular docking, molecular dynamics, ADMET.