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In-silico Identification of Phospholipase A2 Inhibitors from Traditional Medicinal Plants to Treat *Hypnale hypnale* envenomation

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Hypnale hypnale (HH) is one of the six highly venomous snakes in Sri Lanka, responsible for the highest rate of envenomation in the country. Despite this, no specific antivenom is available for its venom, and antivenoms raised for other snake species have proven ineffective. Currently, the symptomatic treatment is the only option available to the patients. Phospholipase A2s (PLA2s), which constitute 40% of the HH venom, are responsible for local effects and represent a key therapeutic target for new antivenoms. This *in-silico* study aimed to identify novel PLA2 inhibitors from traditional medicinal plants as potential therapeutics for HH envenomation. Due to the nonavailability of the protein structure of PLA2 from HH, closely related crystallographic structures of PLA2 from *Trimeresurus stejnegeri* (PDB ID: 4RFP) and two AlphaFold structures of PLA2 from *Calloselasma rhodostoma* (UniProt IDs: Q9PVF4 and Q9PVF2) were used. A total of 966 ligand molecules from eleven traditional medicinal plants in Sri Lanka were docked using the AutoDock Vina docking program. Binding site analysis of the proteins was performed using the PrankWeb server, and ADMET (Adsorption, Distribution, Metabolism, Excretion, and Toxicity) parameters of the phytochemicals were predicted using the SwissADME online server. According to the docking results, ellagic acid, found in *Terminalia chebula* and *Terminalia bellirica*, may have the ability to inhibit PLA2s with favourable ADMET properties. The binding energy of ellagic acid ranged from -8.6 to -7.1 kcal/mol, indicating a high affinity towards all four targets. Receptor-ligand interaction analysis through molecular dynamic simulations using the Schrodinger Desmond program showed hydrogen bond formation with all four protein targets (4RFP GLU 6 residue with 55%, Q9PVF4 TRP 22 residue with 51%, and GLU 22 residue of Q9PVF2 with 98% of the simulation period). The RMSD of 4RFP and Q9PVF2 fluctuated within an acceptable range throughout the simulation period, indicating the stability of the formed complexes. These findings suggest ellagic acid as a potential candidate for treating HH envenomation, warranting further *in vitro* and *in vivo* validation.

Keywords: *phospholipase A2 inhibitors, Hypnale hypnale, antivenom, molecular docking, molecular dynamics*