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A computational approach to identify suitable compounds from Sri Lankan flora envisaging remedial therapy for selected neurodegenerative diseases

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Gaining understanding of neurological disorders affecting a large number of people worldwide, contemplating lower quality of life of patients and their caregivers, would reduce the burden on the society. Neurodegenerative disorders, Alzheimer's (AD), Parkinson's (PD), prion and Huntington's (HD) disorders are known to be caused by main common factors; oxidative stress, protein misfolding and aggregation triggered by metal accumulation. Since the metal ions have to be the prime consideration, chelation therapy is a plausible approach to restore metal balance. Therefore, apt metal binding ligands are categorized from an existing database of 200 chemical compounds identified from Sri Lankan flora, particularly for Fe^{3+}, Cu^{2+}, Zn^{2+} and Al^{3+} ions via a computational approach to be used as lead compounds for drug development.

Screened compounds were evaluated regarding binding free energy with the aid of umbrella sampling molecular dynamics (MD) where 13 numbers of similar simulation system was restrained with harmonic potential along a reaction coordinate (z) assigned. Here, the reaction coordinate is the distance between the center of mass of the ligand and the metal ion. The MD simulations were performed using GROMACS 4.5.1 program on the LINUX operating system. The potential of mean force was computed using the weighted histogram analysis method (WHAM) from the independent trajectories of 13 windows. Upshots of the WHAM technique are given below in the figure.
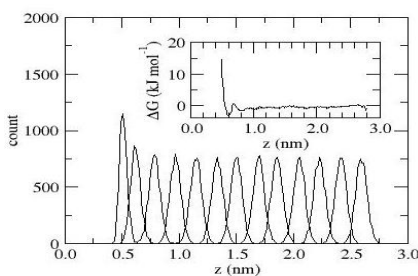
Overlap of neighbouring windows from the Figure ensures there are sufficient windows to cover the entire reaction coordinate space. The free energy change upon binding has been inferred from the inset of the Figure. Free energy calculations reveal number of compounds might possess the potential to alleviate the symptoms of

AD (15 compounds) PD (13 compounds) and prion disease (6 compounds) which should be further analysed in an interdisciplinary way. Furthermore, it indicates no suitable compound for HD from the 200 compounds incorporated in this research. Moreover, this study upholds molecular dynamics simulation output viable within the expected time period.

Keywords: Free energy, Neurodegeneration, Umbrella sampling