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A computational study for the Identification of lead compounds from Sri Lankan flora to treat selected neurodegenerative diseases

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Taxonomy of neurodegenerative diseases (ND) such as Alzheimer's disease (AD), Parkinson's disease (PD) is onerous due to the multifaceted etiology. These disabling illnesses cause immense emotional, physical and economic burden on society hastening the need of disease management. Gathering evidence declares that protein aggregation and oxidative stress mediated by metal accumulation are considered as the major factors involved in neurodegeneration. Since transmutation of metal homeostasis is the rhizome, chelation therapy would be a worthwhile strategy. Thus, potential chelators for the metal ions zinc and aluminium are identified via computational approach to use as lead compounds from an existing database of chemical compounds identified from Sri Lankan flora (http://science.cmb.ac.lk/tools/slflora/) to alleviate the neurological problems.

Aluminium (Al^{3+}) and zinc (Zn^{2+}) complexes were analyzed using umbrella sampling, one of the advanced methods of molecular dynamics that provide the difference in free energy between two states of a molecular system along a reaction coordinate to overcome rare events of sampling in configuration space by restraining the simulation system with harmonic potential. The reaction coordinate is the distance between the center of mass of the ligand and the metal ion. The standard technique weighted histogram analysis method (WHAM) was employed to compute the potential of mean force which is freely available with the GROMACS software package in the LINUX operating system.

Appraisal of the free energy calculations implied that the compounds 2,5-dihydroxy-1,6-dimethoxyxanthone, isoshinanolone carry substantial potential to bind Zn^{2+} and Al^{3+}, respectively, related to reference values. Furthermore, binding units of 1,7-dihydroxy-3-methoxyxanthone with Zn^{2+} and Al^{3+} shows the binding functionality into a single compound. Therefore, these compounds screened using computational endeavour, will set the path for drug design for the treatment and investigation of ND, reducing the wastage of chemicals.

Figure. Structures of 2,5-dihydroxy-1,6-dimethoxyxanthone, isoshinanolone, 1,7-dihydroxy-methoxyxanthone, respectively

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