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In silico evaluation of allosteric mechanism of action of ATP synthase bound with J147: an insight into the allosteric pathway

**INTRODUCTION:The management of Alzheimer's disease (AD) has posed a global burden; most especially in the developed countries of the world as millions of dollar is spent annually to alleviate the disease among old people. Recently it was noted that the progression of Alzheimer's disease involves a decrease in the activity level of mitochondrial ATP synthase in the brain cell which makes it difficult for the brain cells to communicate with each other as well as remain healthy. The discovery J147; a derivative of curcumin, present in the curry spice turmeric is effective in AD treatment. It counters memory loss, enhances the generation of new brain cells, and slows Alzheimer's progression. The breakthrough in the identification of J147 coupled with the recent discovery of mitochondrial ATP synthase as its novel target protein has provided an alternative therapeutic intervention in the control of AD.

METHOD:Here, molecular dynamics (MD) simulations, coupled with free energy calculation were performed to unveil the potential allosteric signal propagation pathway from the allosteric site to the catalytic site in ATP synthase. The lengau cluster CHPC was used to perform the molecular dynamics (MD) simulations for this study. The openMPI 1.8.8 GNU compilers, the GCC 5.1.0, amber modules and the /apps/chpc/chem/amber/14 application code were integrated to access the Amber14 suite. For system parameterization, the ANTECHAMBER and LEAP modules were employed. In analyzing generated MD trajectories, the CPPTRAJ and PTRJ modules were used. Running on 2 nodes and 48 cores, the GPU accelerated PMEMD engine was used.

RESULT:This result revealed that the allosteric modulator J147 induces a slight conformational rearrangement in α subunit which is transmitted to the β subunit as a large conformational change that bring about the rotation of the γ subunit and therefore increases activity in the catalytic site. This conformational transition causes the sliding of β-helix which makes the P-loop to makes contact with the ADP bound at the catalytic site in the β subunit. The discovery of this allosteric mechanism presents a comprehensive view of the regulation of ATP synthase, which is a vital insight for the design of potent allosteric ATP synthase modulators.*emphasized text*

Presenter Biography

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