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Monitoring Insulin Aggregated Structures in the Presence of Epigallocatechin-3-gallate and Melatonin by Molecular Dynamics Simulations

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Epigallocatechin-3-gallate (EGCG) and melatonin ability to inhibit human insulin fibrillogenesis has been recently investigated by means of a number of experimental techniques [1]. Infrared and Raman spectroscopy analysis, after long-term incubation, showed a high content of inter-molecular β-sheet structures in insulin-EGCG complexes. Near-UV experiments, Thioflavin-T fluorescence measurements and Atomic Force Microscopy images clearly revealed that in the presence of EGCG insulin tends to form amorphous, stable ββaggregates rather than fibrils. The same kind of experiments showed that melatonin has no significant inhibitory effects on insulin fibril formation.

We present here, together with the experimental results of [1], an extensive classical MD study [2] of the behavior of six insulin molecules in water in the presence and in the absence of either EGCG or melatonin in order to investigate at atomistic level how these molecules can possibly affect the insulin aggregation propensity. For each model system, we performed three independent simulations (replicas) [3], finding out that, while melatonin does not possess well-defined interaction sites with insulin, EGCG interacts mainly with the residues 11-18 and 24-26 of chain B of the insulin molecules. An important result of our simulations, in excellent agreement with experimental data, is that the shapes of the aggregated structures formed in the three model systems are significantly different depending on whether insulin is in the absence or in the presence of EGCG.

References

[1] Carbonaro, M. et al. Int. J. Biol. Macromol. 2018, 115, 1157–1164.

[2] Vitale, A. and Minicozzi, V. submitted to J. Chem. Inf. Model.

[3] Knapp, B. et al. J. Chem. Theory Comput. 2018, 14, 6127–6138.

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