Analytical and Inorganic Chemistry
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Unraveling Strategies and Mechanisms to Combat Amyloid Aggregation in Alzheimer's Disease: A Comparative *in Silico* Analysis of Curcumin, Kolaflavanone, Tolcapone, and Doxycycline

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Alzheimer's disease, a prevalent form of dementia characterized by brain plaques and tangles, is hypothesized to initiate from the accumulation of amyloid-beta (Aβ) aggregates. However, the underlying pathological mechanisms responsible for Aβ-induced dementia and the development of efficacious therapeutic interventions remain elusive. Amyloid aggregates, formed through the aggregation of diverse proteins because of specific mutations or cellular factors, exhibit a structurally intricate composition enriched with intermolecular β-sheets. Significant attention has been given to natural compounds such as tetracyclines and polyphenols, which exhibit anti-amyloid properties. The rational design of molecules, including β-breaker peptides, whole antibodies, antibody fragments, and drugs targeting transthyretin aggregation, holds promise as potential therapeutic strategies. Integrating computational approaches with biophysical methods is of paramount importance in unraveling the intricate interactions between proteins and drugs, thereby offering valuable insights into developing more potent treatments. Therefore, evaluating the effects and therapeutic efficacy of drugs and nutraceuticals that impede the formation of toxic protein aggregates is imperative while simultaneously exploring methodological aspects to identify novel compounds. The present in Silico study aimed to investigate the potential of various ligands, including curcumin, kolaflavanone, tolcapone, and doxycycline, as anti-amyloid agents capable of inhibiting the aggregation of amyloid proteins. A comprehensive dataset utilizing the Protein Data Bank as a primary resource was generated. Protein-ligand docking was executed following grouping and optimization procedures to investigate the molecular interactions. The resultant outcomes were critically analyzed, and subsequent Molecular Dynamic simulations were performed on the protein-ligand complexes to explore their dynamic behavior and conformational changes over time. Including these specific ligands contributes to a comprehensive examination of natural and synthetic molecules in the ongoing pursuit of effective treatments targeting amyloid-related diseases. Through a meticulous exploration of the interactions and effects of these ligands, this research aims to advance therapeutic strategies aimed at mitigating amyloid aggregation and its associated neurodegenerative conditions.

Literature:

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