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Oleuropein Aglycone as a potent anti-amyloidogenic drug: a computational analysis

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Abstract

Alzheimer's disease (AD) is characterized by the formation of amyloid beta-peptide (Aβ) plaques. These latter induce oxidative stress (OS) and neurotoxicity through different intra/extracellular pathways. Aβ fibrils generate reactive oxygen species (ROS), especially in presence of metal ions, contributing to the oxidative damage of AD brain and disease progression.1,2 Accordingly, antioxidant molecules could counteract this status reducing the severity of AD. Indeed, some natural phenolic compounds decrease ROS production by targeting Aβ fibrils, behaving as Aβ stabilizers or disruptors.3 Generally, disaggregating the preformed fibrils, could reduce the neurotoxicity induced by ROS. Among the phenolic compounds found in the extra virgin olive oil, oleuropein aglycone (OA) produces neuroprotective effects reducing Aβ aggregates by promoting autophagy and by disrupting Aβ fibrils, leading to a decrease of neurotoxicity, ROS and inflammation.4 For investigating the mechanism of action of OA at the molecular level, a computational protocol, employing extensive molecular docking calculation and long-time molecular dynamics simulation (5 μs) for mimicking the system OA/Aβ fibrils, has been developed. Results showed that OA initially interacts with a key motif (LVF-FAED) of Aβ peptide, known to be relevant for fibrils assembly and stability. Afterwards, the long-time MD simulation revealed that OA moved in depth within the Aβ fibrils targeting the mentioned motif in each chain. This movement of OA seems to "cut" the preformed fibrils, causing a significant disruption of the ordered structure. The results demonstrated that OA leads to a structural instability, determining an effective Aβ fibrils disaggregation, due to its insertion within the Aβ preformed fibrils.

According to our investigation OA is a potent anti-amyloidogenic drug able to cause Aβ fibrils disaggregation with consequent reduction of neurotoxicity and OS. Moreover, this work has relevant implication for rationally designing potent multifunctional compounds acting as disease modifying anti-Alzheimer drugs, for the development of innovative anti-AD therapeutics.

Biography

Simone Brogi is an Assistant Professor at the Department of Pharmacy at University of Pisa (Italy). He leads the Computational Pharmacology and Toxicology Unit in the research group of Prof. Vincenzo Calderone. He graduated in 2005 in Biological Sciences from the University of Siena (Italy), where he also received his PhD. in Pharmaceutical Sciences in 2010. From 2011 to 2019 he directed the Molecular Modeling Unit at the Department of Biotechnology, Chemistry and Pharmacy (University of Siena) in the research group of Prof. Giuseppe Campiani. His research activity is focused on computational approaches in drug discovery, with over 85 papers.

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