Contribution ID: **13** Type: **not specified**

The crucial role of stereochemistry in the inhibition of Aβ amyloid growth and toxicity by Silybins

Thursday, 10 March 2022 12:00 (30 minutes)

The self-assembling of the amyloid β (Aβ) peptide into neurotoxic aggregates is considered a central event in the pathogenesis of Alzheimer's Disease (AD). Based on the "amyloid hypothesis" much efforts have been devoted in designing molecules able to halt disease progression by inhibiting Aβ self-assembly. By combining biophysical, biochemical and computational techniques, we investigated the ability of four optically pure components of the natural product Silymarin (Silybin A, Silybin B, 2,3-Dehydrosilybin A, 2,3-Dehydrosilybin B), to inhibit Aβ aggregation. Despite we demonstrated that all the investigated flavonoids prevent the formation of mature fibrils, our results showed that only Silybin B was able to halt the growth of small-sized protofibrils thus promoting the formation of large, amorphous aggregates. Our data suggest that Silybin B interacts mainly with the C-terminal hydrophobic segment 35MVGGVV40 of Aβ40 and its conformation remains predominantly unstructured. By contrast Silybin A interacts preferentially with the segments 17LVFF20 and 27NKGAII32 of Aβ40 which shows a high tendency to form bend, turn and β-sheet conformation in and around these two domains. Moreover in vivo studies in a transgenic C. elegans strain expressing human Aβ, indicated that Silybin B is the most effective of the four compounds in counteracting Aβ proteotoxicity. This study underscores the pivotal role of stereochemistry in determining the neuroprotective potential of Silybins and points to Sil B as a promising lead compound for further development in anti AD therapeutics.

Presenter: Dr SCIACCA, Michele (CNR-Istituto di Cristallografia)

Session Classification: Sessione