Targeting HuD with natural compounds

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RNA-binding proteins (RBPs) play a prominent role in the fate of target messenger RNAs (mRNAs). Among the RBPs, HuD has been intensively studied, it is expressed in nervous tissues, and implicated in the pathogenesis of Alzheimer's disease (AD). The aim of this work is the identification of new ligands able to bind HuD, interfering with its activity. Virtual screening studies were performed using a database of natural compounds and Food and Drug Administration-approved drugs. Starting from about 51000 compounds, 10 promising hits were selected. Considering the commercial availability and the suitability for NMR analysis, 4 compounds were purchased and submitted to saturation transfer difference (STD) NMR investigations, which proved their ability to bind HuD. For each compound, molecular dynamics simulations were performed to deeply investigate the behavior of the ligands in HuD binding site. Finally, a clear correlation between modeling outcomes and STD-NMR results, was observed. It's noteworthy that three of the four identified hits (folic acid, cefazolin, and rosmarinic acid) are natural compounds. Among them, folic acid is the most interesting one, being able to well recognize the HuD binding site. Lastly, cell-based assays were performed, and the biological results support the molecular modeling and STD-NMR data, highlighting the ability of folic acid to recognize and affect HuD expression. These findings could be an important starting point for future treatment of some neurological diseases, in particular for AD [1]. The computational part of this project was carried out in collaboration with Net4Science Academic Spin-Off, (www.net4science.com) and Associazione CRISEA (www.crisea.it).

[1] Ambrosio F.A., et al. Identification of Compounds Targeting HuD. Another Brick in the Wall of Neurodegenerative Disease Treatment. *J. Med. Chem.* **2021**, 64, *14*, 9989–10000.