Current Research in Bioinformatics

Original Research Paper

In Silico Cholinesterase and Monoamine Oxidase Inhibitory Activities of Perillaldehyde and D-Limonene, Main Compounds of Essential Oil of Algerian *Ammodaucus leucotrichus*

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Article history
Received: 26-12-2019
Revised: 11-02-2020
Accepted: 26-02-2020

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Abstract: In a continuation of our previous work for the exploration of novel enzyme inhibitors, molecular modeling was used to inspect the binding mode of perillaldehyde and D-limonene, the major compounds of essential oil of Algerian *Ammodaucus leucotrichus* into the active site pocket of cholinesterase (AChE and BuChE) and Monoamine Oxidase (MAO). The molecular docking was carried out using Molecular Operating Environment (MOE) software package. Docking analysis showed that this compounds (perilladehyde and D-limonene) can interact with both the Catalytic Active Site (CAS) of AChE, BuChE and MAO. For D-limonene, molecular docking showed favorable H-phi interaction with catalytic residue of AchE and BuChE. The perillaldehyde showed best interaction profile with BuChE as compared with compound D-Limonene. The best interaction between perilladehyde and monoamine oxidase was also revealed. This paper shows best correlation between the *in vitro* study and the *in silico* molecular docking study of anti-cholinesterase and anti-monoamine oxidase activities.

Keywords: Acetylcholinesterase, Butyrylcholinesterase, Monoamine Oxidase, Molecular Docking, Perilladehyde, D-limonene

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder that is characterized by progressive deterioration of memory and cognition (Terry and Buccafusco, 2003). The low level of acetylcholine is the most important modification observed in the brain in Alzheimer's patients. Acetylcholine is liberated at the synaptic gap and it is a neurotransmitter which plays a crucial role in memory and cognition (Dall'Acqua *et al*., 2010; Lu *et al*., 2011). It is cleaved by the action of cholinesterase (ChE) enzymes to produce choline and acetate (Quinn, 1987; Sussman *et al*., 1991). There are two types of enzymes (ChE's) that are present throughout the body, acetylcholinesterase (AChE) and Butyrylcholinesterase (BuChE) (Wright *et al*., 1993; Darvesh *et al*., 1998). Currently, the treatment of Alzheimer's disease is based on the cholinergic hypothesis; it is an approach that aims to enhance the cholinergic activity and to increase levels of acetylcholine in the brain by inhibiting cholinesterases which are the key enzymes in the breakdown of acetylcholine (Perry *et al*., 1978).

Monoamine oxidase-A (MAO-A) is an enzyme responsible for specific deamination of Serotonin (5-HT), epinephrine and norepinephrine. It plays an

important role in psychiatric disorders, such as depression and anxiety, whereas Monoamine oxidase-B MAO-B is more specific to other neurotransmitters as phenylethylamine and it is involved in neurological disorders, such as Alzheimer's and Parkinson's disease (Cesura and Pletscher, 1992; Youdim, 1995). In view of the limited number of cholinesterase inhibitors currently available for the treatment of AD, the search for new and potent inhibitors is of significant interest and a progressive area of current research.

Ammodaucus leucotricus belongs to the family Apiaceae, it is an endemic plant and comprises one species in Algeria (Quezel, 1963). *A. leucotrichus* is used by the Algerian Saharan population to treat stomach diseases, fever, vomits, allergies and is also emmenagogue, abortive and aphrodisiac (Maiza *et al*., 2014). Several studies have shown that *A. leucotrichus* is rich in essential oil (Gherraf *et al*., 2013; El-Haci *et al*., 2014).

Chemically, the essential oil of this species is characterized by the presence of perillaldehyde (58.3%) and limonene (23.33%), which were previously studied for their anticholinesterase and monoamine oxidase inhibitory activities (Sadaoui *et al*., 2018). Anti-butyrylcholinesterase and anti-monoamine oxidase activities have been reported for perilladehyde, in contrast, limonene showed only anti-acetylcholinesterase activity (Sadaoui *et al*., 2018).

This work is a continuation of the research work cited above and which consists of an in-depth analysis of the interactions of the tested compounds (perilladehyde and D-limonene) with the enzymes in question. In order to have this better vision and reading of these interactions, molecular docking was carried out.

Methodology

Molecular Docking Study

Molecular docking study was conducted using Molecular Operating Environment (MOE), 2016.08 in order to explore the binding mode of the tested compound (D-Limonene) against Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE) while compound Perillaldehyde against AChE and Monoamine Oxidase (MAO) enzymes. The 3D structures for both compounds were generated using the MOE-builder module of MOE. Next, both the compounds were protonated and were energy minimized using the default parameters of MOE (Gradient: 0.05, Force Field: MMFF94X). The structural coordinates for AChE, BChE and MAO were retrieved from protein databank using PDB code 1acl, 1p0p and 4a79, respectively. All the structure was subjected to MOE for preparation. Next, all the structures were subjected to energy minimization to get the minimal energy conformation of each target. Finally, all the refined structures were used for docking purposes using the default parameters of MOE; Placement: Triangle Matcher, Rescoring-1: London dG, Refinement: Forcefield, Rescoring-2: GBVI/WSA. Before running the docking protocol, we have selected a total of ten conformations for the ligand. The top-ranked conformations based on docking scores were selected for Protein-Ligand Interaction (PLI) analysis.

Results and Discussion

Molecular docking study has been applied to elucidate the interactions occurring in ChE and MAO and their inhibitors. Molecular docking results revealed that both the compounds showed the fit-well mode of binding in the active site of the targeted enzyme. In case of D-Limonene against both the targeted enzyme (AChE and BChE) showed favorable H-phi interaction with catalytic residue, Trp82 against AChE while with Trp84 against BChE (Fig. 1A and 1B), which might have crucial role in inhibition. Both the enzyme shared protein sequence similarity index by more 80%. While in case of compound perillaldehyde against BChE and MAO enzyme (Fig. 1C and 1D), the docking results indicate that against BChE enzyme, compound perillaldehyde showed best interaction profile as compare with compound D-Limonene. The high potency and interaction profile might be due the additional attached electron-donating group (EDG), i.e., OH at *-para* position, which might activate the compound and hence raised the inhibitory potential against BChE enzyme.

Similarly, against MAO enzyme, compound perillaldehyde showed also good interaction profile, i.e., residue Lys296 and Gly58. Overall, these results delineated that perillaldehyde showed best potential for BChE enzyme might be due to the EDG whereas compound D-Limonene lack.

Perilladehyde and limonene was the main components of the essential oil of *A. leucotrichus*. These monoterpènes are present with a percentage of (58.3%) and (23.33%) respectively. The previous study showed that limonene has inhibitory activity only against AchE with an IC50 of 51.6 ug/mL. While, the perillaldehyde showed inhibitory activity against BuChE and MAO with IC50 values of 42.7 ug/mL and 100.4 ug/mL, respectively. The in-vitro results show that perilladehyde had a good inhibitory activity of the enzyme BuChE compared to the inhibition of the enzyme AchE by the limonene. These results were confirmed by the molecular docking (*in silico* study) where it was shown that the perilladehyde-BuChE interaction was better than the AchE-limonene interaction. The in-vitro enzymatic activity best correlates well with the *in-silico* molecular docking study.

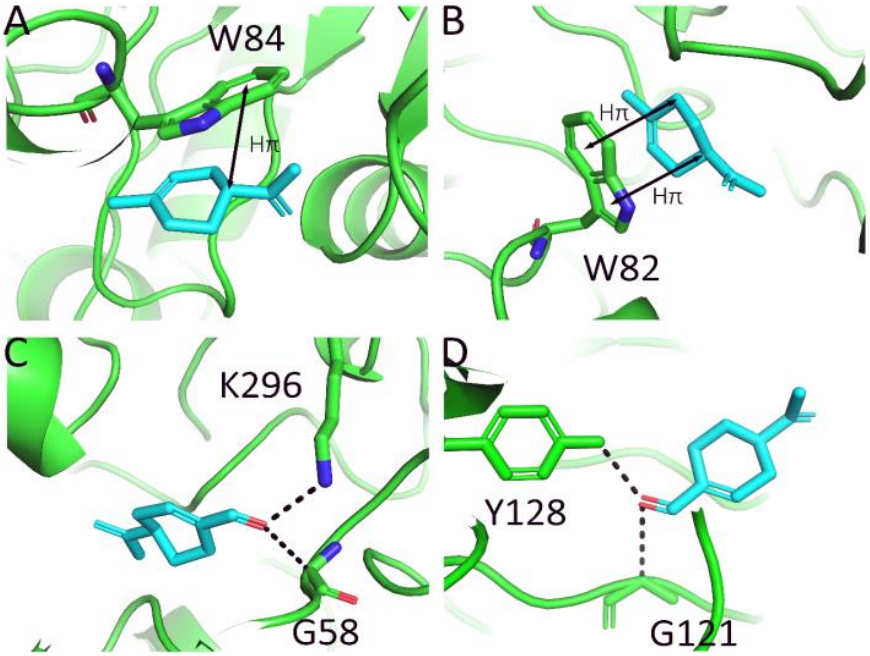

Fig. 1: The PL interaction profiles for D-limonene and perillaldehyde against AChE, BuChE and MAO enzyme. (A) represent the interaction profile for compound D-limonene against AChE; Docking Score -4.87565613 and (B) for BuChE enzyme; Docking Score -4.67808199. (C) Represent the interaction profile for compound perillaldehyde against MAO; Docking Score -5.28108454 and (D) for BuChE enzyme; Docking Score -4.85081863. D-limonene and perillaldehyde were colored into Cyan, while residues into green. Hydrogen bonding is shown in black color dotted lines

Conclusion

The molecular docking was used to determine the interactions between perilladehyde and limonene with the receptor binding-pocket of the cholinesterase (AChE and BuChE) and monoamine oxidase enzymes. Based on this study, it was observed that the D-limonene showed favorable H-phi interaction with catalytic residue of enzymes and perilladehyde also showed good interaction with BChE and MAO enzymes. This work constitutes the beginning of research for a hoped-for objective of arriving at designing new drugs for the treatment of neurodegenerative diseases.

Acknowledgement

Thanks for the "*Direction Générale* de la *Recherche Scientifique* et du *Développement Technologique* (DGRSDT)" *of* Algerian Ministry of Higher Education and Scientific Research for sopporting this work by a PRFU project.

Nesrine SADAOUI acknowledges Nicole BEC and LARROCHE Christian for their contribution to elucidation of cholinesterase and monoamine oxidase inhibitory activities (determination of IC50 values). The authors thank Professor Khemili Amina for her careful reading.

Author's Contributions

Nesrine Sadaoui-Smadhi: Participated in all experiments, coordinated the data-analysis and contributed to the writing of the manuscript.

Souad Khemili-Talbi and Wafa Mokhtari: Designed the research plan (molecular docking), organized the in *silico* study and contributed to the writing of the manuscript.

Rahim Fazal and Wadood Abdul: Participated in moleculat docking and in the analysis of the results.

Souheyla Toubal and Narimen Benhabyles: Participated in biological activities of *A. leucotrichus*.

Karim Arab and Khettal Bachra: Designed the research plan (the experimental study) and organized the study.

Conflicts of Interest

The authors declare no conflict of interest.

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