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

1Nesrine Sadaoui-Smadhi, 1Souad Khemili-Talbi, 2Wadood Abdul, 3Souheyla Toubal, 3,Wafa Mokhtari, 3Narimen Benhabyles, 3Karim Arab, 5Khettal Bachra and 6Rahim Fazal

1Département de Biologie, Faculté des sciences, Université M’hamed Bougara de Boumerdes, Avenue de l’indépendance, Boumerdes 35000, Algeria
2Department of Biochemistry, Abdul Wali Khan University, Mardan, Khyber Pakhtunkhwa, Pakistan
3Laboratoire de Valorisation et de Conservation des Ressources Biologiques (VALCORE), Département de Biologie, Faculté des Sciences, Université de Boumerdes, Boumerdes, Algeria
4Unité Computational Biology and Bioinformatics (service 3BIO, EPB), Université Libre de Bruxelles, CP 165/61, avenue F. Roosevelt 50, 1050 Bruxelles, Belgium
5Laboratoire de Biotechnologies Végétales et Ethnobotanique, Faculté des Sciences de la Nature et de la Vie, Université de Bejaia, Bejaia 06000, Algeria
6Department of Chemistry, Hazara University, Mansehra, Khyber Pakhtunkhwa, Pakistan

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 these compounds (perillaldehyde 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 perillaldehyde 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, Perillaldehyde, 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.

Ammadoraucus leucotrichus belongs to the family Apicaeae, 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 (Maïza 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 (23.3%), 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 perillaldehyde, 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 (perillaldehyde 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 (BuChE) 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, BuChE 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, Refscoring-1: London dG, Refinement: Forcefield, Refscoring-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 BuChE) showed favorable H-phi interaction with catalytic residue, Trp82 against AChE while with Trp84 against BuChE (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 BuChE and MAO enzyme (Fig. 1C and 1D), the docking results indicate that against BuChE 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 BuChE 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 BuChE enzyme might be due to the EDG whereas compound D-Limonene lack.

Perillaldehyde and limonene was the main components of the essential oil of A. leucotrichus. These monoterpenes are present with a percentage of (58.3%) and (23.3%) 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 perillaldehyde 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 perillaldehyde-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 perillaldehyde 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 perillaldehyde 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.

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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 molecular 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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