STEM Scholars program 2014

The Role of Water in Drug-Protein Recognition

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Abstract

Caspases belong to a group of intracellular cysteine proteases that plays an active role during cell apoptosis. Their active role in this process make them a good target for drug design. From this family of enzymes, caspase-3 could be highlighted due to its association with neuronal death in degenerative neural diseases like Alzheimer. From the list of promising molecular inhibitor for caspase-3, flavonoids seems to be a viable option for this enzyme. Our results shows that the flavonoids binds to the active site of caspase-3 in a configuration that maximize the displacement of unfavorable water molecules from the active site previously determined by Hydration Site Analysis (HSA). Acknowledging the importance of water in ligand binding process.

Introduction

Apoptosis is the process of programmed cell death which occur in many multicellular organisms. From all the proteins involved on the process, caspases play an important role in cell apoptosis as they act as the executioners. The caspases belong to a family of intracellular cysteine proteases. These enzymes use the sulfur atom in cysteine to perform the cleavage reaction in protein degradation. Caspase-3 is a member of this family of enzymes and a predominant caspase associated with neuronal death in Alzheimer's Disease. During apoptosis, caspase-3 is responsible for chromatin condensation and DNA fragmentation. The active role of the caspase-3 in make it a perfect target for drug design.

Flavonoids are molecules that can be found in almost all plants. In the human body, they work as antioxidants, affect anti-inflammatory mechanisms and act directly as antibiotics. Flavonoids such as luteolin, quercetin, and kaempferol have been proven to bind to caspase-3. In the present study we use Docking and Hydration Site Analysis (HSA) to evaluate the use of flavonoids as inhibitors for caspase-3. We also evaluate the role of water in the ligand binding process and the possibility to use water as a tool to enhance the binding affinity of the ligands.

Experimental Design

- Visual Molecular Dynamics (VMD) was used to make the molecular representation.
- AutoDdock Vina and AutoDock Tools (ADT) was used to perform the computational simulation of the binding orientation and the protein-ligand binding energies calculation.
- Hydration Site Analysis (HSA) was used to identify highly localized water molecules on the active site of the enzyme that could increase the inhibitor affinity by their removal upon binding. (Taken from unpublished previous results)
- The ligand interaction representation were made using the PDBsum website.

Results

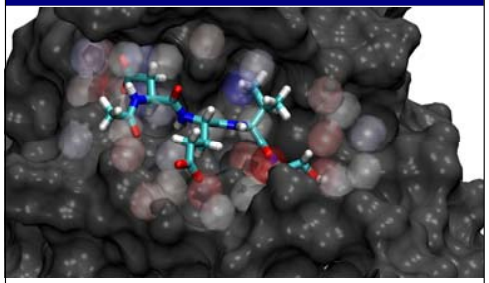

Figure 1-A. Caspase-3 surface (gray), HSA waters (transparent) spheres and the ligand Ac-DEVD-Cho in stick.

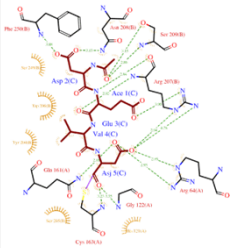

Figure 1-B. Structure of Ac-DEVD-Cho and ligand-protein interactions with the active site of Caspase-3 (pdbid:2H5I). Ligand in red and close interacting residues in black. Hydrogen bonding interactions denoted by the green lines and orange "eyeslashes" denote Non-bonded contacts residues.

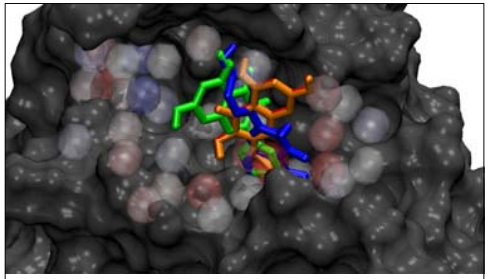

Figure 2. Caspase-3 surface (gray), HSA waters (transparent) spheres and the docked flavonoids in stick.

Flavonoid	Affinity (Kcal/mol)
Kaempferol	-6.5
Luteolin	-7.1
Myricetin	-7.2
Quercetin	-7.1

Table 1. Auto-Dock Vina binding energy results for each flavonoids.

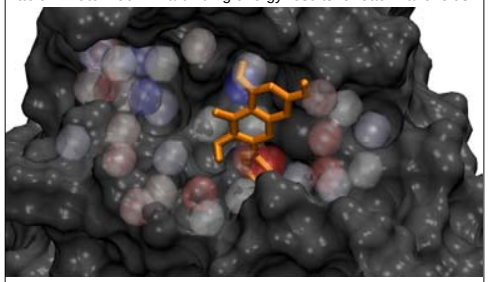

Figure 3-A. Caspase-3 surface (gray), HSA waters (transparent) spheres and Myricetin (orange) as docked by Auto-dock Vina.

Figure 3-B. Structure of Myricetin and ligand-protein interactions with the active site of Caspase-3 (pdbid:2H5I). Ligand in red and close interacting residues in black. Hydrogen bonding interactions denoted by the green lines and gold "eyeslashes" denote Non-bonded contacts residues.

Conclusion

The results shows that water has a key role in the binding mode of the ligands in the enzyme active site. As all the ligand try to bind to places with highly localized water molecules as determined by the hydration site analysis (HSA). This results also reveals that water can be used to plan modifications to the binding molecules in order to increase its binding affinity.

References

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Acknowledgments

I would like to show my deeply appreciation and thanks to Dr. Philip (BCC Chemistry Dean) for giving me this opportunity. Also I would like to thanks Dr. Rachlin (STEM Program Director) for his challenging questions every Friday. Finally, thanks to Prof. Kurtzman (Lehman Mentor) and Anthony Cruz (Lehman PhD Candidate), my deepest gratitude for their patience in this molecule structure learning process.