Computational Docking of Caffeine Derivatives and Binding to Xanthine Oxidase

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Abstract

Building on previous research on XOD ligand docking, this study aims to test a caffeine derivative compound structure similar to Urate and Allopurinol that would exhibit a similar binding mechanism to XOD with high affinity. These modified caffeine molecules could potentially serve as an alternative drug compounds to Allopurinol, which is an effective inhibitor for XOD. To investigate this possibility, we performed computational ligand docking and binding analysis in the XOD active site. Our findings indicate that a standard caffeine molecule exhibits poor binding affinity in comparison to standard uric acid values. However, caffeine derivatives with carboxylic acid side groups and methyl groups display similar binding mechanisms to XOD. These modified caffeine molecules could serve as alternative drug compounds to Allopurinol, an effective inhibitor for XOD.

Introduction

Xanthine Oxidase (XOD) is a two-subunit enzyme that is involved in the oxidation of hypoxanthine, a byproduct of purine catabolism, to uric acid in the bloodstream. This enzyme is crucial in the regulation of uric acid levels and plays a role in the development of gout, a type of arthritis characterized by the overproduction of uric acid. Allopurinol is a drug used to treat hyperuricemia by inhibiting XOD activity and thereby decreasing uric acid production. Caffeine is a natural alkaloid that is widely consumed in coffee and tea. It is known to have a multitude of metabolic effects, including its ability to inhibit XOD activity. This study aims to investigate the potential of caffeine derivatives as XOD inhibitors.

Methods

For this study, Xanthine Oxidase (XOD) and standard uric acid FDB files were obtained from Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB-PDB). Allopurinol, caffeine, and caffeine derivative ligand FDB files were built using Spartan '18 V1.2.0. To prepare for data collection, a single XOD subunit structure was isolated and the associated functional group and coenzyme were removed. Computational docking to a native XOD subunit was conducted using the AutodockTools-1.5.6 program, and docking visualization was performed using PyMOL, Tussil GL align  Console. To calibrate the AutodockTools software, ligand docking coordinates were calculated. Three programs were used to determine binding mode, XOD active site interactions, and binding affinity values (kcal/mol). Root-mean-square deviation (RMSD), which served as a confidence interval, was also determined.

Results

Below are results of Autodock Vina computations of docked Uric Acid, Allopurinol, Caffeine, and Caffeine Derivatives in XOD. Results consist of binding affinity (kcal/mol), RMSD, and binding model structurally similar to Urate and Allopurinol that would exhibit a similar binding mechanism to XOD with high affinity. These modified caffeine molecules could serve as alternative drug compounds to Allopurinol, which is an effective inhibitor for XOD. To investigate this possibility, we performed computational ligand docking and binding analysis in the XOD active site. Our findings indicate that a standard caffeine molecule exhibits poor binding affinity in comparison to standard uric acid values. However, caffeine derivatives with carboxylic acid side groups and methyl groups display similar binding mechanisms to XOD. These modified caffeine molecules could serve as alternative drug compounds to Allopurinol, an effective inhibitor for XOD.

Conclusion

In conclusion, caffeine derivatives exhibit a poor binding interaction with XOD. Although there are some similarities in the binding modes of caffeine and uric acid in the XOD active site, there are significant differences. Future studies are needed to investigate the potential of caffeine derivatives as XOD inhibitors.

References


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