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Investigation Of The Binding Affinities Of Natural Compounds To Specific Protein Targets Through Docking

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Abstract

Natural products have long served as valuable sources of bioactive molecules, many of which exhibit potent therapeutic properties with minimal adverse effects. Development of drug discovery processes that are computational; has seen the molecular docking becoming an indispensable method for the rapid prediction of protein-ligand interactions and the selection of good natural candidates for further studies. In this paper, we looked at how well and in what way the natural polyphenolic compound **ellagic acid (EA)** interacted with Poly (ADP-ribose) polymerase 10 (PARP10), a cancer-causing enzyme mono-ADP-ribosyltransferase that is very much involved in the tolerating of replication stress, inflammatory processes, and tumor growth. The goal was to find out if EA is a PARP10-inhibitor with potencies corresponding to anticancer drugs.

Molecular docking studies were conducted using AutoDock Vina 1.2.7, after very careful preparation of the protein and ligand done by UCSF Chimera, Chem3D, and AutoDockTools. Layout of the required grid parameters was done using AutoGridFR to have precise identification of the catalytically active binding region. A total of ten docking modes were subjected to exploration with a very high degree of exhaustiveness to make sure that the sampling of the poses was correctly done. The analysis of the post-docking results was done using the BIOVIA Discovery Studio Visualizer where characterization of the hydrogen bonding, hydrophobic contacts and π–π interactions was done.

EA showed a very strong binding affinity of –9.554 kcal/mol, which was greater than that of the re-docked co-crystallized inhibitor Veliparib (–8.5 kcal/mol) and this fact pointed out the validity of both the protocol and the possible superiority of EA as a binder.Interaction mapping revealed stabilizing hydrogen bonds with Tyr919 and Ala911, along with π–π stacking involving Tyr932 and His887, highlighting excellent structural complementarity within the PARP10 catalytic site. Overall, the results indicate that ellagic acid may act as a promising natural inhibitor of PARP10 with potential implications in cancer therapy. While docking provides a strong theoretical

foundation, further validation through molecular dynamics simulations, enzymatic inhibition assays, and cellular studies is required to confirm its biological relevance and therapeutic potential.

Introduction

Natural products are substances or chemical compounds that are naturally produced by living things [1], including plants, animals, and microorganisms [2]. Humans have used natural resources as their main source of food, shelter, and healing since ancient times. In recent decades, extensive research has been conducted on natural herbs in an effort to find and develop new therapeutic agents that are good for human health and have few or no negative side effects [3].

The therapeutic value of compounds found in plants has been known for ages, resulting in their utilization in homes and in clinics for the treatment of many ailments ranging from common headache to serious conditions such as wounds. Several medications, including quinine (Cinchona spp.), artemisinin (Artemisia annua), and taxol (Taxus brevifolia), which are antimalarial medications, have already been obtained from nature [4]. 60% of cancer drugs and 75% of infectious disease drugs are also derived from natural products [5].

Molecular docking is a computational approach that anticipates the affinity of ligands for receptor proteins [6].The three main objectives of molecular docking are essentially virtual screening, pose prediction, and binding affinity estimate. The docking results are significantly impacted by the preparation of the protein and ligand. Prior to docking, proteins and ligands are produced independently using automated processes (such as adding hydrogens and charges) [7]. Following docking the ligand against the protein, the interactions are examined. The anticipated interaction energy is used to determine each ligand's binding affinity, and the ligands are ranked according to their affinity scores [6].

Molecular docking is widely been used for predicting binding affinities of protein and ligand [8]. Drug discovery is a labor-intensive and time-consuming process that involves choosing, designing, and optimizing compounds based on target proteins unique to a disease. The core and basis of drug discovery is the process of predicting the interactions between chemicals and proteins, which includes drug-target interaction (DTI), drug-target binding affinity (DTA), drug-target interaction sites, and drug bioactivity on proteins [9]. Consequently, it often takes over ten years to find a new medication, and its commercialization costs between two and three billion dollars [10]. Drug discovery is now quicker, less expensive, and more effective thanks in large part to molecular docking [11].

In today's drug development process, molecular docking has become an essential tool, particularly for taking use of the enormous chemical variety found in natural products. Rich sources of pharmacophores with demonstrated bioactivity are frequently found in natural substances [7, 12]. By quickly predicting how tiny compounds will attach to protein targets, in silico docking helps researchers identify the most promising possibilities [13]. Docking speeds up the early stages of drug discovery by rapidly modeling thousands of molecules and assisting in the prioritization of natural products that should be tested in a lab [7, 12].

Docking predicts the binding affinity of ligands to receptor proteins and is, therefore, a powerful technique in discovering new drugs [14]. To put it briefly, docking offers an affordable in silico filter for ranking natural substances according to their capacity to bind target proteins [15].In this work we focus on protein target of high biomedical significance: PARP10. This plays a crucial role in disease pathogenesis and is of great interest as a drug target. **PARP10** is a mono-ADP-ribosyltransferase in the poly (ADP-ribose) polymerase (PARP) family. PARP10 is overexpressed in many human

tumors and actively promotes oncogenic processes. Actually, PARP10 promotes proliferation of cancer cells by releasing the stress from DNA replication and allowing the cells to tolerate the damage[16]. Its enzymatic activity can ADP-ribosylate important signalling proteins. PARP10 inhibits NF-κB signalling by ADP-ribosylating NEMO [17]. Thus, PARP10 bridges DNA repair and inflammatory pathways. The evidence suggests that PARP10 plays a role in the tumor's ability to survive and escape the immune system; hence, the inhibition of PARP10 could be a new strategy for cancer treatment [16].

The natural compound, ellagic acid, selected for this study, has broad pharmacological profiles that fit the above target very well. Ellagic acid (EA) is a polyphenolic antioxidant that is usually found in several fruit (e.g. pomegranates, berries) and nuts [18]. It is well known for its antioxidant, anti-inflammatory, antimicrobial and antimutagenic activities. In cancer models, EA suppresses proliferation and promotes apoptosis in several tumour cell lines, including gastric, liver, pancreatic, and breast cancers [19]. EA's capacity to scavenge reactive oxygen species and inhibit pro-inflammatory signalling, such as NF-κB, is responsible for these effects [19]. Importantly, EA's anticancer activity includes inhibition of DNA damage response pathways. EA docks into kinases (like VEGFR2) and reduces their activity, thereby blocking proliferative signaling. Ellagic acid binds strongly to immune checkpoint proteins [20]. Together, these findings illustrate that EA is a **multifunctional anticancer phytochemical**. Because of its low toxicity and wide spectrum of bioactivity, EA has been categorized as a potential lead for the production of safer anticancer drugs [18, 20].The association of this protein with the aforementioned natural ligand is directed by complementary pharmaceutical factors. Ellagic acid and PARP10 are both associated with cancer biology. PARP10 is a driver of tumor cell proliferation and survival [21], and EA has well-established anticancer effects [22].

Material and Methods

System Configuration and Software Used

Molecular docking studies focusing on the selected compound were carried out on a standard personal computer with an Intel® Core™ i7-8650U CPU @ 1.90 GHz (2.11 GHz boost), 16 GB RAM, 477 GB SSD, and Intel® UHD Graphics 620. Moreover, the computer worked on a 64-bit Windows 10 operating system. The experimental docking was performed using AutoDock Vina 1.2.7 [23] to find out the binding affinities and interaction profiles between the natural compound and the selected protein target.

Ligand and Protein Retrieval

The three-dimensional structure of the ligand, Ellagic Acid (EA), was taken from the PubChem database (CID: 5281855) in SDF format [24], and the crystal structure of Poly (ADP-ribose) polymerase 10 (PARP10), a mono-ADP-ribosyltransferase enzyme of high oncogenic importance, was acquired from the RCSB Protein Data Bank (PDB) in legacy PDB format [12]. The selection of both structures was done considering their biological relevance, structural resolution, and reported functional significance in the research of cancer-related pathways.

Protein and Ligand Preparation

Prior to docking, the protein structure was prepared using UCSF Chimera 1.9. All non-standard residues, heteroatoms, and solvent molecules were removed in order to prevent steric hindrances and enhance the accuracy of docking, only the specific chain containing the active site was kept [25]. The processed protein model was saved in

PDB format for further handling. The ligand structure was processed using Chem3D 23.1.1 to obtain the lowest energy conformation, which is then exported in PDB format. Afterward, the protein and ligand structures were converted to PDBQT format using AutoDockTools 1.5.6. During this conversion, polar hydrogens were added to the protein, and Gasteiger charges were assigned to both the macromolecule and ligand to create a more favorable electrostatic environment for docking calculations [12, 26].

Grid Generation and Docking Configuration

The AutoGridFR (AGFR) system was used to depict the active binding site of PARP10, where a three-dimensional grid box was designated to include the area of ligand binding [27]. The grid box center coordinates (x, y, and z) were then calculated and recorded for the configuration file based on the residues of the protein's catalytic site. To ensure full coverage of the active site cavity, the grid box dimensions were fixed at 22 × 22 × 22 $Å^3$. To achieve reliable sampling and docking pose convergence, the energy range was set to 4, exhaustiveness to 100, and number of binding modes were set to 10 for all docking simulation.

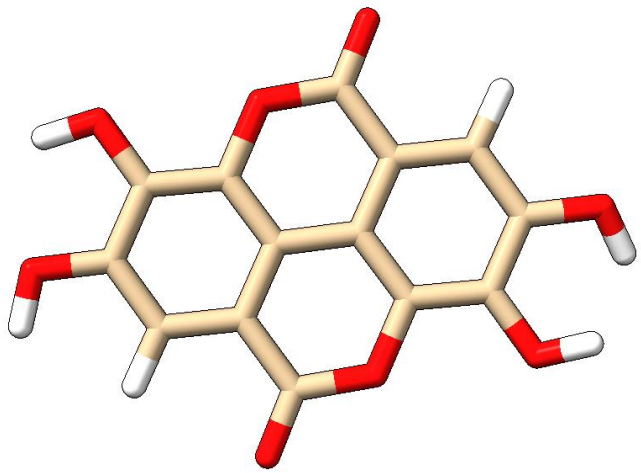

Figure 1. Ellagic Acid structure

Docking Simulation

AutoDock Vina 1.5.6 is the docking engine used to perform the actual docking simulations. Vina is a widely used, open-source docking program known for its efficiency and accuracy in predicting binding poses [6]. AutoDock Vina was employed through command line execution. The ligand was regarded as flexible, enabling all rotatable bonds to freely explore conformational space, while the protein was treated as a rigid receptor. The docking results produced binding affinity scores (in kcal/mol) and corresponding binding poses for the ligand within the target active site.

Post-Docking Analysis

In the post docking analysis, the conformation with the lowest binding energy was assigned the highest rank [28]. BIOVIA Discovery Studio Visualiser v17.2 was used to visualize and comprehend the resulting complex [29], analyzing hydrogen bonding, hydrophobic interactions, and π-π stacking between the ligand and amino acid residues of PARP10. To verify the accuracy of the expected binding orientation and interaction profile, the docked structure was compared with known PARP inhibitor.

Results and Discussions

Docking score

Molecular docking of the natural compound **Ellagic Acid (EA)** with the selected protein target **Poly (ADP-ribose) polymerase 10 (PARP10)** was successfully performed using **AutoDock Vina 1.2.0**. The range of binding affinities was quite wide in the simulated docking and the most stable conformation was found with a binding energy of –9.554 kcal/mol that was rated as very strong and favorable interaction of EA with the active site of PARP10. Based on the lowest binding energy, which corresponds to high stability and minor deviation amongst the predicted conformations, the top-ranked pose was selected.

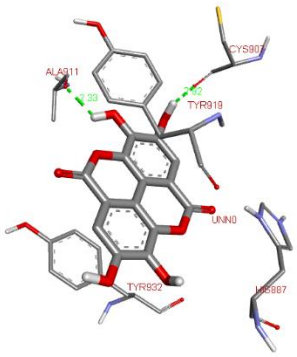

Figure 2. PARP10-Ellagic acid complex in Discovery studio

Validation of Docking Protocol using Re-Docking

To validate the docking protocol and confirm that the chosen grid parameters and search settings reliably reproduce known ligand–protein interactions, the co-crystallized inhibitor present in the downloaded PARP10 structure (Veliparib) was first removed and re-docked into the same binding site using identical grid coordinates (X 43.62, Y 18.308, Z 80.674), grid size (22 × 22 × 22 Å), exhaustiveness (100), energy range (4) and number of output modes (10). The re-docking procedure returned a best-scoring pose for Veliparib with an affinity of **–8.5 kcal·mol⁻¹**, confirming that the docking setup locates a plausible, energetically favorable binding mode for a known PARP inhibitor under the present conditions. The visual inspection of the re-docked Veliparib gave a very good correspondence with the crystallographic ligand orientation which indicated the appropriateness of the selected grid center and sampling parameters for the subsequent ligand evaluation.

Comparative Binding Analysis: EA vs Veliparib

Benchmark results contrasted with EA docking and revealed that ellagic acid gains a better predicted binding energy (–9.554 kcal·mol⁻¹) than the re-docked Veliparib (–8.5 kcal·mol⁻¹). The high affinity for EA indicates that it fits into PARP10's binding region effectively, possibly forging several stabilizing interactions with important amino acid residues.

Protein-Ligand Interaction

The docked complex visualization by BIOVIA Discovery Studio Visualizer v17.2 showed that EA is very well sited in the catalytic domain of PARP10, forming hydrogen bonds and π–π stacking interactions with crucial residues taking part in

ligand recognition and catalysis. The interaction map reveals that Tyr919 and Ala911 create rather strong hydrogen bonds with EA at lengths of 2.32 Å and 2.42 Å, which respectively means that EA gets stabilized quite well within the active site. Also, π–π stacking interactions were detected with the aromatic residues Tyr932 and His887, whereas Cys907 and Tyr919 make a contribution through van der Waals contacts to the binding complementarity of the complex that is enhanced. All these interactions create a situation in which there is a strong network of non-covalent forces that are mainly responsible for the observed high binding affinity.

Structural Complementarity

The EA and PARP10 binding cavity being very close in terms of structural complementarity implies that the compound could possibly interfere with the enzyme's mono-ADP-ribosylation activity, thereby modulating the major processes like DNA damage repair and replication stress response.In addition, the stable hydrogen bonding with Tyr919 and Ala911 residues, which are located near the catalytic loop of the enzyme, could either hinder substrate access or modify the conformational dynamics that are required for ADP-ribose transfer. This discovery may account for possible downstream suppression of DNA repair signaling. The π–π interactions with Tyr932 and His887 constitute additional reinforcement to hydrophobic stabilization, which is a typical feature of the most powerful PARP inhibitors. These strong non-bonded interactions not only highlight the high structural compatibility of ellagic acid with PARP10's active site but also advocate its being the lead candidate for anticancer drug design.

Overall Evaluation and Future Directions

Overall, the docking results show that ellagic acid has stable binding interactions and a strong affinity for PARP10, indicating a promising inhibitory potential. These computational findings are a theoretical foundation for the subsequent in vitro validation and structure–activity relationship (SAR) studies which are directed toward the optimization of EA derivatives with better potency and selectivity towards PARP10. Thus, the present docking study contributes to understanding the molecular basis of ellagic acid's anticancer properties and its possible role in targeting DNA repair-associated enzymes.

Conclusion

The molecular docking analysis demonstrated that ellagic acid exhibits a strong binding affinity toward the catalytic domain of PARP10, surpassing that of the co-crystallized inhibitor. This result indicates the nature of ellagic acid as a PARP10 natural inhibitor and also gives support to its possible therapeutic significance.In summary, the computational outcomes provide a theoretical justification for considering ellagic acid a promising lead compound in the further drug development process. However, as docking studies are only predictive, the findings require validation using molecular dynamics simulations, enzyme inhibition experiments, and cellular research to establish their efficiency and biological relevance.

References

Ouyang, L., et al., Plant natural products: from traditional compounds to new emerging drugs in cancer therapy. Cell proliferation, 2014. **47**(6): p. 506–515.

Rakshit, G., et al., Molecular docking and molecular dynamics in natural products-based drug discovery, in Phytochemistry, computational tools and databases in drug discovery. 2023, Elsevier. p. 195–212.

Mir, R.H., et al., Therapeutic potential of plant-derived flavonoids against inflammation, in Recent developments in anti-inflammatory therapy. 2023, Elsevier. p. 279–293.
Dzobo, K., The role of natural products as sources of therapeutic agents for innovative drug discovery. Comprehensive pharmacology, 2022: p. 408.
Boldi, A.M., Libraries from natural product-like scaffolds. Current opinion in chemical biology, 2004. **8**(3): p. 281–286.
Agu, P.C., et al., Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. Scientific reports, 2023. **13**(1): p. 13398.
Asiamah, I., et al., Applications of molecular docking in natural products-based drug discovery. Scientific African, 2023. **20**: p. e01593.
Gromiha, M.M. and K. Harini, Protein-nucleic acid complexes: Docking and binding affinity. Current Opinion in Structural Biology, 2025. **90**: p. 102955.
Zhao, L., et al., A brief review of protein–ligand interaction prediction. Computational and Structural Biotechnology Journal, 2022. **20**: p. 2831–2838.
Mohamed Abdul Cader, J., et al., Ensembling methods for protein-ligand binding affinity prediction. Scientific Reports, 2024. **14**(1): p. 24447.
Muhammed, M.T. and E. Aki-Yalcin, Molecular docking: principles, advances, and its applications in drug discovery. Letters in Drug Design & Discovery, 2024. **21**(3): p. 480–495.
Jafari, S. and J. Bojarska. Molecular Docking Study of Natural Compounds Targeting the β2-Adrenergic Receptor (β2-AR). in Medical Sciences Forum. 2025. MDPI.
Rajendran, A.T., et al., Selection of potential natural compounds for poly-ADP-ribose polymerase (PARP) inhibition in glioblastoma therapy by in silico screening methods. Saudi Journal of Biological Sciences, 2023. **30**(7): p. 103698.
Agu, P., et al., Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. Scientific Reports, 2023. **13**.
Bugnon, M., et al., SwissDock 2024: major enhancements for small-molecule docking with Attracting Cavities and AutoDock Vina. Nucleic Acids Research, 2024. **52**(W1): p. W324–W332.
Schleicher, E.M., et al., PARP10 promotes cellular proliferation and tumorigenesis by alleviating replication stress. Nucleic acids research, 2018. **46**(17): p. 8908–8916.
Zhu, H., et al., The critical role of PARPs in regulating innate immune responses. Frontiers in immunology, 2021. **12**: p. 712556.
Ceci, C., et al., Experimental evidence of the antitumor, antimetastatic and antiangiogenic activity of ellagic acid. Nutrients, 2018. **10**(11): p. 1756.
Čižmáriková, M., et al., Ellagic acid and cancer hallmarks: insights from experimental evidence. Biomolecules, 2023. **13**(11): p. 1653.
Othman, B., et al., Comprehensive pharmacokinetic profiling and molecular docking analysis of natural bioactive compounds targeting oncogenic biomarkers in breast cancer. Scientific Reports, 2025. **15**(1): p. 5426.
Schleicher, E.M., et al., PARP10 promotes cellular proliferation and tumorigenesis by alleviating replication stress. Nucleic Acids Res, 2018. **46**(17): p. 8908–8916.
Ceci, C., et al., Experimental Evidence of the Antitumor, Antimetastatic and Antiangiogenic Activity of Ellagic Acid. Nutrients, 2018. **10**: p. 1756.
Eberhardt, J., et al., AutoDock Vina 1.2. 0: new docking methods, expanded force field, and python bindings. Journal of chemical information and modeling, 2021. **61**(8): p. 3891–3898.

Kim, S., et al., PubChem 2025 update. Nucleic acids research, 2025. **53**(D1): p. D1516–D1525.
Pettersen, E.F., et al., UCSF Chimera—a visualization system for exploratory research and analysis. Journal of computational chemistry, 2004. **25**(13): p. 1605–1612.
Morris, G.M., et al., AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. Journal of computational chemistry, 2009. **30**(16): p. 2785–2791.
Mhatre, S. and V. Patravale, Drug repurposing of triazoles against mucormycosis using molecular docking: a short communication. Computers in Biology and Medicine, 2021. **136**: p. 104722.
Malakar, V., et al., Deciphering Potent Protein Tyrosine Phosphatase-1B Inhibitors Through In silico Molecular Docking, MMGBSA, and Molecular Dynamics. ChemistrySelect, 2025. **10**(4): p. e202403082.
Sharma, S., A. Sharma, and U. Gupta, Molecular Docking studies on the Anti-fungal activity of Allium sativum (Garlic) against Mucormycosis (black fungus) by BIOVIA discovery studio visualizer 21.1. 0.0. 2021.