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Research Article

Amodiaquine as Topoisomerase I Inhibitors: A Computational Approach

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ABSTRACT

Aim: The aim of this project is to utilize *in silico* approaches to identify potential anticancer agents by targeting the human topoisomerase I-DNA complex (PDB ID: 1A35), a critical enzyme involved in DNA replication and repair. The study focuses on evaluating the binding efficacy of repurposed drugs, including antifungal compounds, to expedite anticancer drug discovery. **Materials and Methods:** Protein Preparation: The 3D structure of the human topoisomerase I-DNA complex (PDB ID: 1A35) was retrieved, refined, and energy-minimized for molecular docking. Ligand Preparation: Irinotecan, Topotecan (known chemotherapeutics), and Amodiaquine (antifungal drug) were drawn in ChemDraw Ultra 8.0, converted to 3D structures, and energy-minimized using Chem3D Pro 8.0. Drug-Likeness Screening: Ligands were assessed via Lipinski's Rule of Five to evaluate pharmacokinetic suitability. Molecular Docking: AutoDock Vina in PyRx was employed for docking ligands to the protein. Binding interactions were visualized using Biovia Discovery Studio 2024 Client. **Results:** Docking scores revealed binding energies of -8.4 kcal/mol for Irinotecan, -7.6 kcal/mol for Topotecan, and -7.0 kcal/mol for Amodiaquine. Amodiaquine demonstrated stable interactions with key residues of topoisomerase I, suggesting potential inhibition of DNA-enzyme complexes. All ligands adhered to Lipinski's Rule of Five, confirming favorable drug-like properties. **Conclusion:** This *in silico* study highlights Amodiaquine as a promising repurposed candidate for anticancer therapy, with notable binding affinity and interactions with topoisomerase I. While Irinotecan exhibited the strongest binding, Amodiaquine's efficacy underscores the potential of antifungal drugs in oncology. Further *in vitro* and *in vivo* validation is warranted to confirm its therapeutic utility.

Keywords: Amodiaquine, Anticancer agents, AutoDock Vina, *in silico* study, Lipinski's Rule of Five, Molecular docking, Topoisomerase I.

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INTRODUCTION

New anticancer drugs that target the disease's molecular pathways must be developed because cancer is still a major worldwide health concern.[1] The unchecked growth and multiplication of aberrant cells is a hallmark of cancer, a complicated and multidimensional disease.[2] The National Cancer Institute estimates that 9.6 million deaths from cancer occurred in 2018, making it the second most common cause of death globally.[3] Cancer is still a serious public health issue despite tremendous advancements in its study and treatment, which emphasizes the need for more research and better treatment approaches.[4]

During critical biological processes like transcription, recombination, and replication, essential enzymes called topoisomerases regulate the topological states of DNA.[1,2] Topoisomerase 1 is crucial for lowering torsional stress because it causes transient single-stranded breaks in DNA. Since dysregulation of Topo 1 activity has been connected to the development of cancer, it is a desirable target for new therapeutic developments.[1,3] Several topo 1 inhibitors, such as camtothecin and its derivatives, have demonstrated noteworthy efficacy as anticancer medications. However, the associated side effects and increasing drug resistance necessitate the development of novel inhibitors.[5]

The docking analysis of amodiaquine against the topo 1A35 protein is presented in this paper. In order to predict the medication Amodiaquine's binding affinity against this enzyme, docking was done. Additionally, the docking can produce valuable data for additional research on amodiaquine's anticancer properties.[6,7]

MATERIALS AND METHODS

Materials

In the present study, many software's and bioinformatics tools were used. Table 1 lists the software's applications (Figure 1).

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Methods

Preparation of Protein

The Protein Data Bank provided Protein (pdb) ID 1A35, which is accessible at www.pdp.org, in PDB format. Human DNA Topoisomerase 1 forms a complex with 3 chains and 518 residues of DNA in the 1A35 protein. Topo I is its synonym. MOE software was then used to minimize the energy of the protein (Figure 2).

Ligand Creation

The protein PDB 1A34 was docked with amodiaquine. Chemdraw Ultra 8.0 was used to draw the ligands' two-dimensional structure. Chem3D Pro 8.0 was then used to convert it to a 3D structure and minimize it before it was saved in PDB format.

Docking Studies

The orientation of inhibitors in the enzyme's binding pocket and the interaction between the ligands and the enzyme are revealed by docking studies. Drugs and enzymes are examples of compounds that dock together. Free energy stimulations can also be used to assess binding affinities and molecular dynamics during these docking processes.

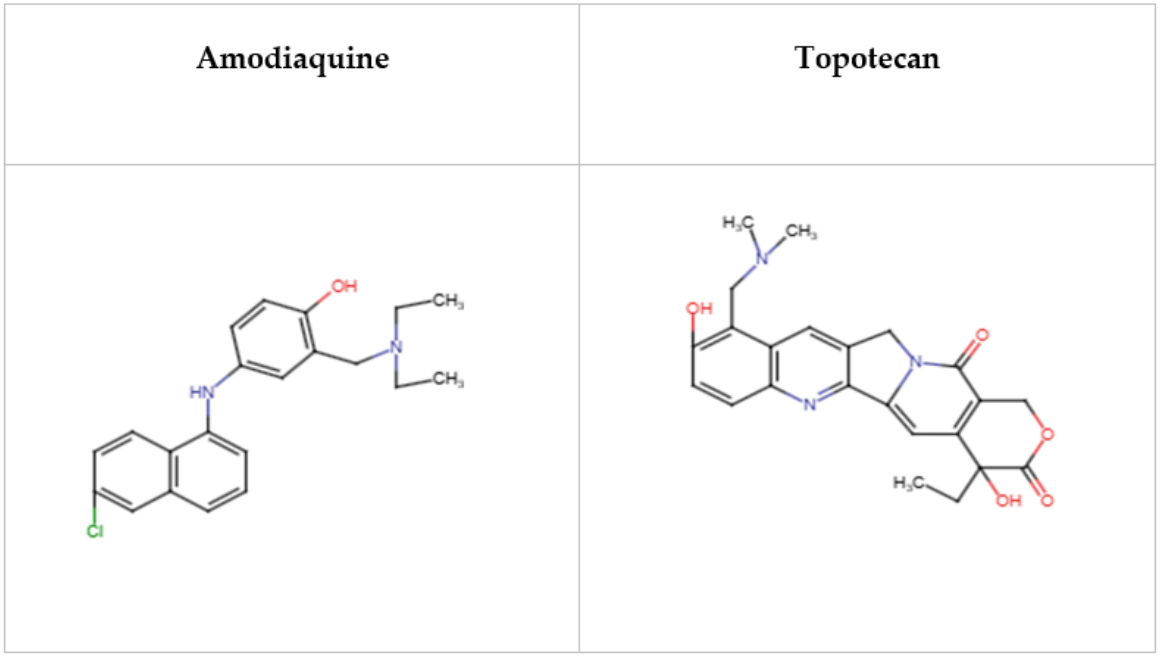

Figure 1: Structure of amodiaquine and topotecan.

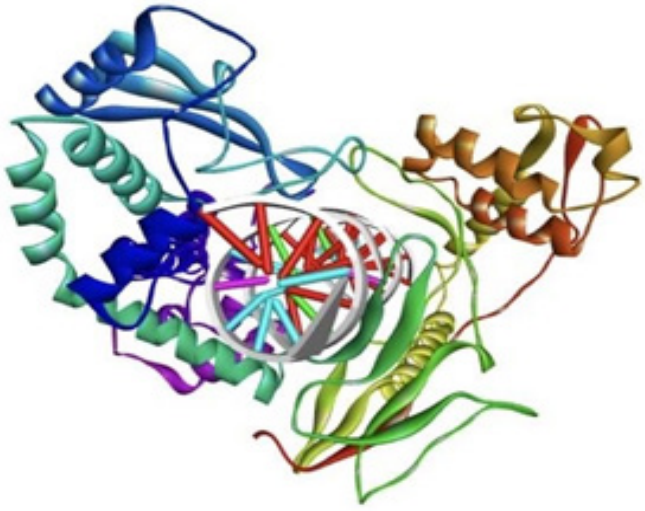

Figure 2: Structure of protein (PDB ID: 1A35).

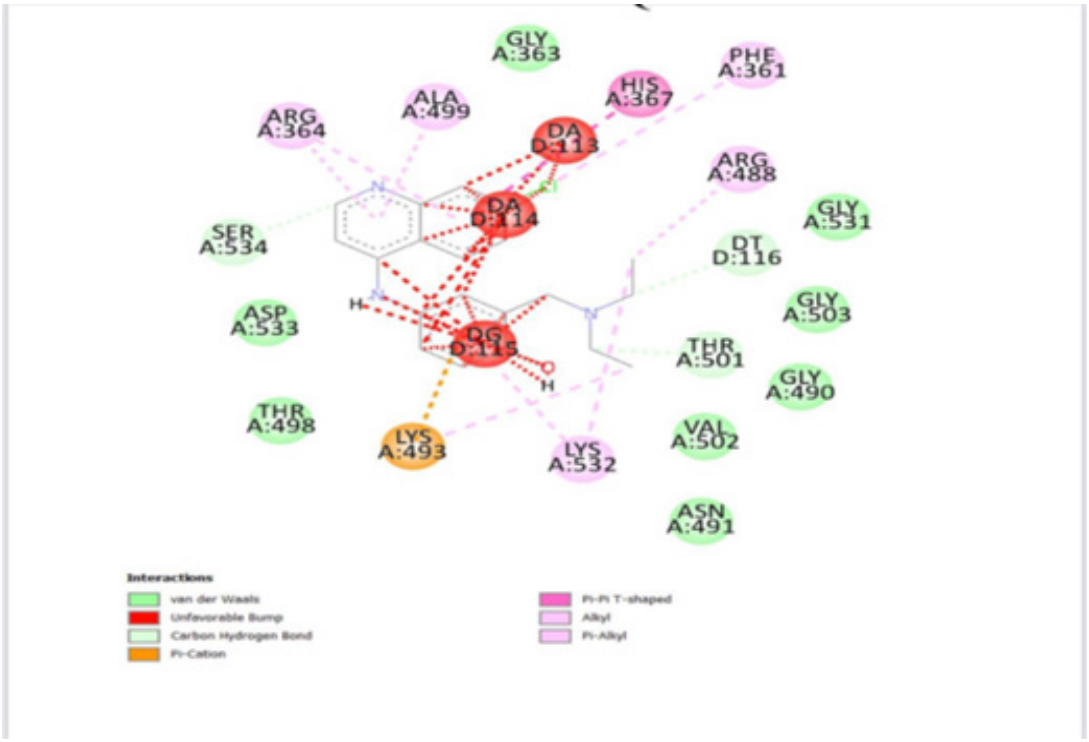

Figure 3A: Binding interaction of Amodiaquine with aminoacids on binding sites. (a) 2D structure of ligand Amodiaquine interaction with binding site of protein 1A35.

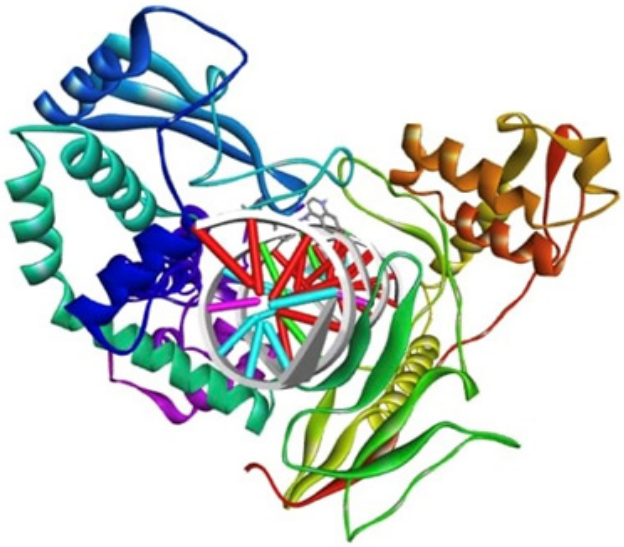

Figure 3B: Binding interaction of Amodiaquine with aminoacids on binding sites. . (b) 3D structure of ligand interaction with binding site of protein 1A35.

Amodiaquine was used as a ligand in this investigation, and human topoisomerase I complexed with DNA as a receptor. Autodock vina PyRx was used to carry out these ligand-protein docking investigations. Based on its anticancer properties, Amodiaquine targets the structure of protein 1A35 (Figure 3). Using Biovia Discovery Studio, the suggested compounds were visualized with protein after water molecules and ligands were extracted from it (Figure 4).

RESULTS AND DISCUSSION

Docking

The scoring function for the docking run is the binding affinity Ebind among the ligand and protein. Autodockvina performed chemical reactions with PyRx using bioactive compounds.[8] Both the medication development and repurposing processes depend on the compound's interaction with the target protein.[9] The most often used technique to evaluate the accuracy of docking

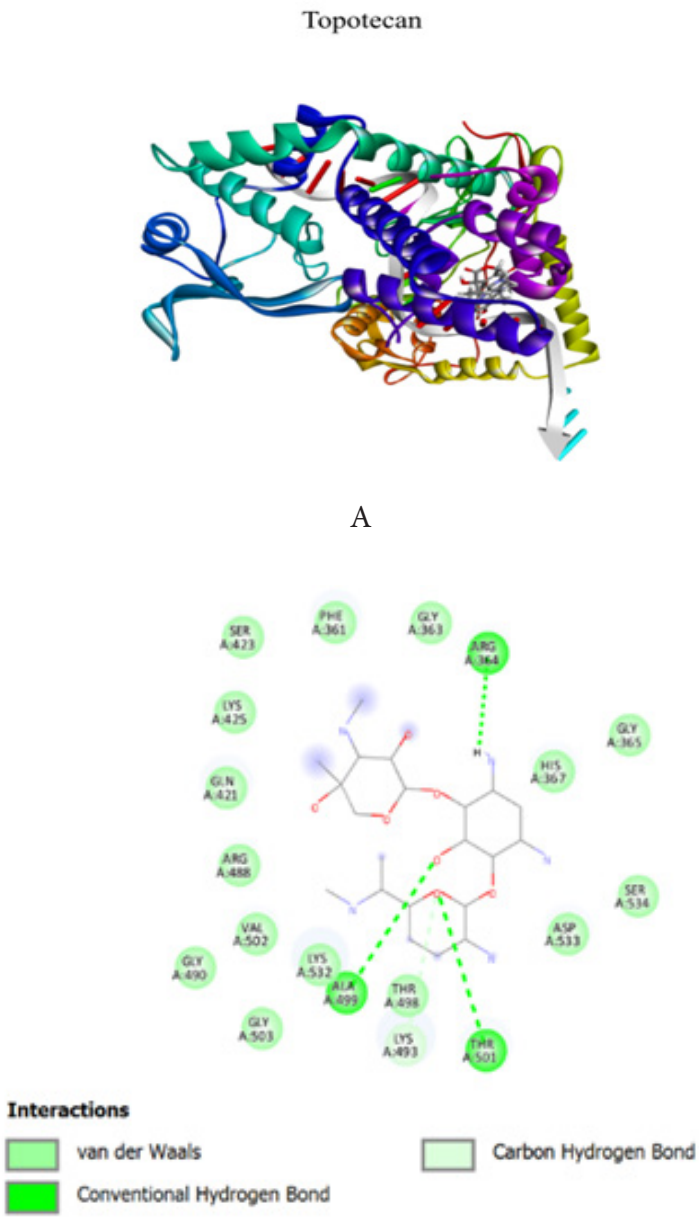

Figure 4: Binding interaction of Topotecan with aminoacids on binding sites. (b) 3D structure of Topotecan interaction with binding site of protein 1A35.

is to calculate the Root Mean Square Deviation (RMSD) for the chemical from its original position within the intricate response after the receptor molecules have been overlaying.[10] Autophagy inhibition and SCD1 suppression work together to produce an additive anti-tumor influence both in the laboratory and in animal.[11] The binding energy value of the drug amodiaquine, as determined by docking, is comparable to that of a typical medicine that has more negative effects than amodiaquine. It was discovered that amodiaquine's binding energy value ranged from -6.4 to -7.6 kcal/mol-1. Amodiaquine's binding energy was determined to be -7.6 by comparing the docking data with that of topotecan -8.4.[12]

Significantly, AQ causes cytotoxicity, inhibits colony formation, inhibits cell migration, decreases the volume of the 3D spheroid, triggers apoptosis, stops the advancement of the cell cycle, inhibits the expression of genes linked to cancer, and inhibits autophagy via inducing the LC3BII protein.[13,14] Amodiaquine binds Hsp27 and exhibits important interaction patterns with BVDU.[15] The interactions between the amino acid residues and the ligand Amodiaquine through pi-alkyl bonds, alkyl bonds, and Vander Waals forces emphasize the compound's competitive inhibitory activity.[16,17] Although DR is a promising trend, more research is need to guarantee its efficacy and safety for the novel indications.[18,19] Using a computational approach,

Table 1: List of software's and their utilities.

Sl. No.	Software	Utilities
1	ChemDraw Ultra 8.0	It is a program for drawing ligands' two-dimensional structures.
2	Chem3D Pro 8.0	Software for developing three-dimensional representations and reduce ligand energy.
3	MOE (Molecular Operating Environment)	Software to determine the active chain for reducing protein energy.
4	PyRx Virtual Screening Tool	Autodockvina Software
5	Biovia Discovery Studio	Finding the protein's active location and reviewing the docking results.

it was discovered that amodiaquine, an FDA-approved malaria treatment drug with a known security and drugs profile, was also an anticancer agent applicant. It also suppressed chemical resistance in a number of myeloma cancer cell line by blocking the heat shock protein 27 chaperone function.[20]

CONCLUSION

Uncontrolled cell proliferation and the ability to invade or spread to other sections of the body are characteristics of the complex collection of disorders known as cancer. Genetic abnormalities that impair regular cellular processes cause this unchecked growth, which can result in tumor development and, in certain situations, metastasis. Repurposing the antimalarial medication amodiaquine as a powerful anticancer agent is significant since creating new drugs is a laborious and time-consuming procedure. When Amodiaquine was docked in this investigation, it was discovered to have a high affinity and the least amount of energy, much to the common medication Topotecan. Amodiaquine's energy value, as determined by Autodockvina PyRx, was found to be -7.6. This leads us to believe that Amodiaquine exhibits anticancer activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of Interest.

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