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# MOLECULAR ASSESSMENT OF DNA BINDING MODES OF SELECTED ANTI-CANCER DRUGS

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## ABSTRACT

The interaction of anti-cancer drugs with DNA plays an important role in understanding their mechanism of action, therapeutic efficacy, and potential toxicity. The present study will focus on the molecular assessment of DNA binding modes of selected anti-cancer drugs to elucidate the nature and strength of their interactions with DNA. The investigation will examine whether the selected drugs interact with DNA through intercalation, groove binding, electrostatic association, or other possible binding mechanisms. Spectroscopic techniques such as UV–Visible absorption and fluorescence spectroscopy will be employed to evaluate changes arising from drug–DNA interactions and to determine binding characteristics. Complementary molecular approaches, including molecular docking, will be considered to identify probable binding sites and characterize intermolecular interactions such as hydrogen bonding, π–π stacking, and electrostatic interactions. The study will provide insights into the structural basis of DNA recognition by selected anti-cancer agents and may contribute to a better understanding of their biological activity, selectivity, and therapeutic potential.

***Keywords:*** Anti-cancer drugs; DNA binding; Molecular interactions; Drug–DNA interaction; Intercalation; Groove binding; UV–Visible spectroscopy;

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## INTRODUCTION

Because many anti-cancer medications aim to hinder DNA replication, transcription, and cell proliferation by interfering with its structure and function, DNA is a major molecular target for many of these treatments. An important factor determining a drug's toxicity, therapeutic efficacy, and biological activity is the way it interacts with DNA. Some anti-cancer medications attach to DNA in a variety of ways, such as electrostatic interactions with the phosphate backbone, binding inside the major or minor grooves, or intercalation between base pairs. As a result, learning the molecular basis of a drug's activity requires molecular evaluation of these interactions. The binding affinity and conformational changes linked to drug-DNA interactions may be better understood with the use of spectroscopic methods like fluorescence spectroscopy and ultraviolet-visible absorption. Hydrogen bonding, π-π stacking, and other intermolecular interactions may be better understood and potential binding sites can be located via molecular docking. This work aims to shed light on the interaction processes and therapeutic value of chosen anti-cancer medications by molecularly assessing their DNA binding modalities.

## REVIEW OF LITRETURE

Ahmed, Benzir et al., (2022) Various forms of binding, including intercalation, groove binding, covalent binding, and others, allow metal-complexed anticancer medicines to interact with DNA nucleobase pairs (AT and GC). All types of anticancer agents rely on the binding mechanism of DNA base pairs via either the minor or major grooves, as metal complexes connect with DNA nucleobases with tremendous affinity. When interacting with DNA base pairs, ligands in metal complexes are also crucial; ligands directly engage DNA via several interacting mechanisms. In order to attach to DNA, anticancer medicines often use planar ligands and N-based aromatics with less sterically hindered structures, since these ligands are well-suited to the intercalation and groove binding mechanisms. To compute the real interactions in drug-DNA complexes, quantum mechanical simulations could be highly useful due to the enormous complexity of experimental inquiry into drug-DNA nucleobase complexes. When trying to determine how metal-complexed anticancer drugs really interact with DNA nucleobase, quantum mechanical methods like density functional theory (DFT) could be an invaluable resource. In this study, we examined the correct mechanism of interaction between drug-DNA complexes using metal complexes with N-based

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aromatic ligands as anticancer drugs.

Ahirwar, Hemant et al., (2022) It is well-known that the process of discovering new drugs is difficult, time-consuming, costly, and complex. According to estimates, the typical time and money needed to produce a new medicine via the conventional drug development pipeline is roughly 12 years and $2.7 billion USD. The pharmaceutical sector is facing the difficult and pressing dilemma of how to accelerate the development process of new drugs while decreasing the expense of research. In recent years, computer-aided drug discovery (CADD) has grown in prominence as a viable option for improved, more efficient, and less expensive medication development. The fast expansion of computational drug discovery techniques, particularly those pertaining to anticancer medicines, has had a notable and impressive effect on the creation of anticancer drugs and has also yielded useful insights into cancer treatment.

Pandya, Nirali et al., (2021) Several oncogene promoter regions and telomeric ends of chromosomes are thought to include G-quadruplex (G4) motifs, which are higher-order secondary structures. One promising approach to the creation of anti-cancer medicines is the stabilisation of G-quadruplex structures in proto-oncogene promoters by use of certain small compounds. One of the anti-cancer drugs that has been licensed by the FDA is methotrexate. It is known to decrease the action of dihydrofolate reductase (DHFR), which ultimately leads to cell death. We used a variety of bio-physical methods to learn how Methotrexate interacts with G-quadruplex motifs found in proto-oncogenes and the telomeric region (tel22) in this work. Among all G-quadruplex and duplex DNA, Methotrexate exhibited the most binding affinity and specificity for bcl-2 G4 ($Kd^1$=9nM). Methotrexate has a greater stabilising effect on bcl-2 G4, according to circular dichroism melting study. The interaction with the G4 structure was shown to be stacking, according to molecular docking and dynamic simulation research. In a cellular-based study, Methotrexate showed a greater level of toxicity to A549 lung cancer cells compared to other cancer cell types including PC-3, HeLa, and HepG2. Results from quantitative RT-PCR and western blotting show that A549 lung cancer cells treated with Methotrexate were able to stabilise the G-quadruplex motif and downregulate bcl-2 transcription and translation. Finally, this paper sheds fresh light on Methotrexate's anti-cancer effectiveness and gives important information on its alternative molecular mechanism for cancer therapy.

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Abu-Dief, Ahmed &Alsehli, Mousa (2020) An essential component of all biological processes, deoxyribonucleic acid (DNA) regulates cellular chemistry. Although it is considered a non-specific target of cytotoxic medicines, it is the molecular target of several medications used in cancer therapies. One of the most crucial parts of biological research in the pharmaceutical and drug discovery processes is understanding how medicines interact with DNA. Also, when it comes to rationally designing chemotherapeutics, knowing which targets to target is crucial, especially when it comes to creating compounds for cancer therapy. It is possible to piece together the interaction mechanism by observing the pre- and postsigns of drug-DNA interaction. The identification of novel DNA-targeting medicines and the measurement of existing ones are two further potential applications of this interaction. The interaction mechanism between anti-cancer medications and DNA may be better understood with the use of novel approaches that provide light on rational drug design. The goal of this review is to get a better understanding of the many interaction parameters that affect the ability and selectivity of anticancer medications to interact with DNA by studying these drugs, DNA, and the processes of interaction. Furthermore, several experimental methods for detecting and assessing the DNA interactions of anticancer medicines were also brought forth.

Ahmadi, Farhad et al., (2019) Metronidazole (MTZ) and zinc ion complexes were produced and studied using UV-Vis, X-ray crystallography, X-ray Fourier transform infrared (FT-IR), $^{1}$H-NMR, and thermal gravimetric-differential thermal analysis (TG-DTA). Results from experiments conducted on SKNMC, A549, MCF-7, and MCDK cell lines demonstrated that the synthesised complex exhibited a significant level of cytotoxic potential. Examining the intrinsic binding constant and establishing thermodynamic characteristics of the complex over the DNA, in conjunction with an in silico molecular modelling approach, helped to provide light on the process of cell cytotoxicity and oxidative stress as they related to complex binding to calf thymus-DNA. This was accomplished by docking the complex over the DNA structure and optimising it at the B3LYP/LANL2DZ level. The findings showed that the contact between the metronidazole-zinc complex and DNA occurred via electrostatic interaction with the phosphate backbone and hydrogen binding, respectively.

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## MOLECULAR DOCKING AND STRUCTURAL ANALYSIS OF DNA–DRUG COMPLEXES

One useful computational method for studying the molecular basis of interactions between some anti-cancer medications and DNA is molecular docking. The current investigation will make use of molecular docking to forecast the likely locations, orientations, and conformations of the chosen medication molecules inside DNA structures for binding. Whether the medications mostly interact via intercalation, minor-or major-groove binding, or interactions with the negatively charged phosphate backbone may be better understood with the use of this study. The purpose of studying complexes that were formed by docking is to identify the kinds and intensities of the intermolecular interactions that stabilised the drug-DNA complexes. Topics such as hydrogen bonding, interactions between aromatic drug moieties and DNA base pairs, van der Waals forces, electrostatic interactions, hydrophobic contacts, and π-π stacking will get special focus. In order to evaluate the relative binding tendencies of the chosen anti-cancer medications, we will compare their binding poses and docking scores. Structural visualisation will make it much easier to study DNA structural changes, drug orientation, bond lengths, and interacting nucleotides. In order to get a thorough knowledge of drug-DNA recognition, the results of molecular docking will be compared with experimental spectroscopic measurements, where relevant. By bringing all of the data sets together, we may better understand the molecular factors that control DNA binding and, maybe, why the chosen anti-cancer drugs have different biological effects. Docking studies provide structural information that might help us understand how anti-cancer drugs work, how selective they are, and how effective they are.

## BIOLOGICAL SIGNIFICANCE AND THERAPEUTIC IMPLICATIONS OF DNA BINDING

DNA binding is a key biochemical process by which a number of anti-cancer medications work. Crucial cellular functions including chromosomal segregation, replication, transcription, and repair may be disrupted when medications interact with DNA, which is necessary for storing and transmitting genetic information. Such interference has the potential to cause cell-cycle arrest, apoptosis, or other types of cancer cell death by preventing the growth of rapidly dividing cancer cells. The binding mechanism, affinity, specificity, and structural features of the medicinal

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molecule have a significant impact on the biological outcomes of DNA binding. While intercalating agents may modify DNA conformation by inserting between neighbouring base pairs, groove-binding compounds can do so by recognising particular structural areas of DNA without significantly disrupting the base-pair arrangement. Another factor that may affect DNA stability and drug localisation is electrostatic interactions with the phosphate backbone.

Since the intensity and type of drug-DNA interactions may impact drug potency, selectivity, pharmacological activity, and toxicity, understanding these binding processes has substantial therapeutic implications. Although enhanced anti-tumour action may result from strong or extended DNA binding, this may raise the risk of harm to normal cells, which is one of the negative consequences. To better understand why anti-cancer medications with similar structures have varying degrees of efficacy, molecular characterisation of DNA binding might be useful. In order to learn about binding affinities, preferred binding sites, and the intermolecular interactions that cause complex formation, spectroscopic investigations, molecular docking, and structural analysis may be used. This data could help in the hunt for structural markers linked to efficient DNA recognition and targeted anti-cancer effects. New therapeutic agents with enhanced effectiveness and decreased toxicity may be developed and optimised with the help of knowledge about DNA-drug interactions. Therefore, evaluating DNA binding is crucial for understanding the molecular mechanism of current anti-cancer therapies. It also lays the groundwork for rational drug design, therapeutic optimisation, and the creation of tailored anti-cancer treatments in the future.

## CONCLUSION

To better understand the molecular processes that drive the therapeutic efficacy of some anti-cancer medications, it is necessary to conduct molecular analyses of their DNA binding modalities. Intercalation, groove binding, electrostatic association, and other stabilising interactions will be the focus of the research, which aims to characterise the type, strength, and mechanism of interaction between the chosen medicines and DNA. We can learn a lot about changes in DNA structure and drug-DNA binding properties from spectroscopic investigations, and we can find out a lot about important interactions like hydrogen bonding, π-π stacking, electrostatic forces, and van der Waals interactions from molecular docking. To fully


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comprehend how DNA-drug complexes are formed, it is necessary to correlate experimental and computational results. The results will help shed light on why the chosen anti-cancer drugs have varied levels of biological activity and DNA recognition capabilities. As a whole, the research will add to our knowledge of how drugs interact with DNA, which might help in the fight against cancer by leading to more targeted treatments with less side effects and better therapeutic effectiveness.

## REFERENCES

1. Ahmed, Benzir&Barukial, Pratyashee& Bezbaruah, Mrinal & Ali, Ibrahim & Bezbaruah, Bipul. (2022). A comparative DFT study of some N-based aromatic ligand metal complexes as anticancer agents and analysis of their mode of interaction with DNA base pair. Journal of the Indian Chemical Society. 99(4) 1-9.
2. Ahirwar, Hemant & Kurmi, Gabbar & Khan, Rubeena & Khare, Basant & Jain, Anushree & Jain, Prateek & Thakur, Bhupendra. (2022). Review on QSAR using Anticancer Drug. Asian Journal of Dental and Health Sciences. 2(4) 59-63.
3. Pandya, Nirali & Jain, Neha & Kumar, Amit. (2021). Interaction analysis of anti-cancer drug Methotrexate with bcl-2 promoter stabilization and its transcription regulation. Gene Reports. 23(1) 20-29.
4. Abu-Dief, Ahmed &Alsehli, Mousa. (2020). DNA Interaction of Drug Molecules for Cancer Treatment. 2(2) 12-16.
5. Ahmadi, Farhad &Shabrandi, Ako & Hosseinzadeh, Leila & Azizian, Homa. (2019). Two DNA binding modes of a zinc-metronidazole and biological evaluation as a potent anti-cancer agent. Nucleosides, Nucleotides and Nucleic Acids. 38(7) 449-480.
6. Venugopal, Sneha & Sharma, Vikas & Mehra, Anuradha & Singh, Iqubal& Singh, Gurdeep. (2022). DNA intercalators as anticancer agents. Chemical Biology & Drug Design. 100(4) 580-598.
7. Uemura, Masako & Yoshikawa, Yuko & Yoshikawa, Kenichi & Sato, Takaji & Mino, Yoshiki &Chikuma, Masahiko & Komeda, Seiji. (2013). Second- and higher-order structural changes of DNA induced by antitumor-active tetrazolato-bridged dinuclearplatinum(II) complexes with different types of 5-substituent. Journal of inorganic biochemistry. 127(7) 169-174.

**Online ISSN: 2456-1495**
**CODEN (USA): JSLOBJ**

8. Goftar, Masoud &Moradikor, Nasrollah & Kor, Zahra. (2014). DNA INTERCALATORS AND USING THEM AS ANTICANCER DRUGS. International journal of Advanced Biological and Biomedical Research. 2(3) 812-822.
9. Tyagi, Gunjan & Jangir, Deepak & Singh, Parul & Mehrotra, Ranjana. (2010). DNA Interaction Studies of an Anticancer Plant Alkaloid, Vincristine, Using Fourier Transform Infrared Spectroscopy. DNA and Cell Biology. 29(11) 693-699.
10. Alshaikh, Nouf & Zaki, Mehvash&Sharfalddin, Abeer & Hussien, Prof Mostafa. (2023). Synthesis, Structural Characterization, DNA/HSA Binding, Molecular Docking and Anticancer Studies of Some D-Luciferin Complexes. Arabian Journal of Chemistry. 16(9) 1-24.
11. Agudelo, Dana & Bourassa, Philippe & Bérubé, Gervais. (2016). Review on the binding of anticancer drug doxorubicin with DNA and tRNA: Structural models and antitumor activity. Journal of photochemistry and photobiology. B, Biology. 158(4) 274-279.



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