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DNA Minor Groove Molecular Docking and Molecular Dynamics Simulations of the Oolong Tea Glycoside Chafuroside A

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Abstract

Cancer remains a leading global health challenge, driving the urgent need for the discovery and development of novel anti-tumor compounds. This study employs a comprehensive computational approach to evaluate the therapeutic potential of chafuroside A, a natural glycoside, by investigating its interaction with DNA and assessing its pharmacokinetic and toxicological properties. The three-dimensional structure of chafuroside A was obtained, and its binding affinity to DNA was analyzed through molecular docking using PatchDock and FireDock. To further validate the stability of the resulting complex, a 100 ns molecular dynamics simulation was performed. The results demonstrated that chafuroside A exhibits a superior global binding energy and forms a more stable complex with DNA, characterized by a greater number of hydrogen bonds, compared to the reference chemotherapeutic drug mitoxantrone. These in silico findings suggest that chafuroside A is a highly promising anti-tumor agent, potentially outperforming established treatments. However, to confirm its efficacy and safety, the compound warrants further rigorous experimental validation through in vitro and in vivo studies.

Keywords: Molecular docking, MD simulation, ADMET, DNA, Minor groove, Genotoxicity

Introduction

Cancer is a major health problem in the United States, where it is projected that more than 1.9 million new cases and over 600,000 deaths will occur in 2022. Lung cancer is the leading cause of cancer death, accounting for about 350 deaths per day (Siegel *et al*., 2022). Therefore, there is an urgent need to screen a wide range of natural and synthetic compounds to discover novel and effective cancer therapeutics. The current drugs are not highly specific and have adverse side effects. Moreover, the cancer cells can develop multi-drug resistance, which is one of the main reasons for the failure of conventional cancer therapy (Wijdeven *et al*., 2016; Bray *et al*., 2018; Kebe *et al*., 2025).

There are various types of cytotoxic drugs that have been used in cancer treatment. These drugs can act on DNA by forming either covalent (irreversible) or noncovalent (reversible) bonds. Noncovalent genotoxic drugs can be further classified, based on their mode of action, into two categories (Godzieba & Ciesielski, 2020; Guillen & Pereira, 2024; Lee *et al*., 2025), as shown in **Figure 1**.

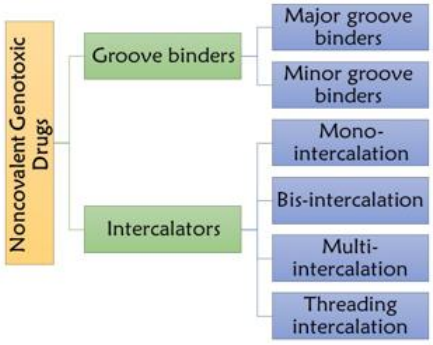

Figure 1. Classification of noncovalent genotoxic drugs.

The structure of DNA creates two grooves that differ in their size and shape: the minor groove and the major groove. The minor groove is narrower and shallower, with a width of 6.7 Å and a depth of 8.2 Å, while the major groove is wider and deeper, with a width of 11.6 Å and a depth of 8.5 Å (Khan *et al*., 2012; Khan *et al*., 2024). These differences affect the binding preferences of different biomolecules to DNA. For example, most proteins bind to the major groove, while most small molecules bind to the minor groove. The small molecules that bind to the minor groove tend to favor AT-rich regions, because they have less steric hindrance than GC-rich regions (Hasanzadeh & Shadjou, 2016; Csep *et al*., 2024; Conti *et al*., 2025). Additionally, they have many rotatable bonds that allow them to adjust their conformation to fit the binding site (Cai *et al*., 2009; Njoroge & Odhiambo, 2025).

Distamycin and netropsin are natural small molecules that bind to the minor groove and have anti-tumor activity. However, they also have a major drawback: they are cytotoxic to both cancerous and healthy cells (Barrett *et al*., 2013; Snodin & McCrossen, 2024; Raza *et al*., 2025). Therefore, they are not suitable candidates for

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cancer therapy, but they have inspired scientists to search for similar compounds with better efficacy and lower toxicity. In this study, we applied computational methods to evaluate the potential of a natural glycoside, chafuroside A, as a minor groove binder and an anti-tumor agent. We also predict its pharmacokinetic and toxicological properties using in silico tools.

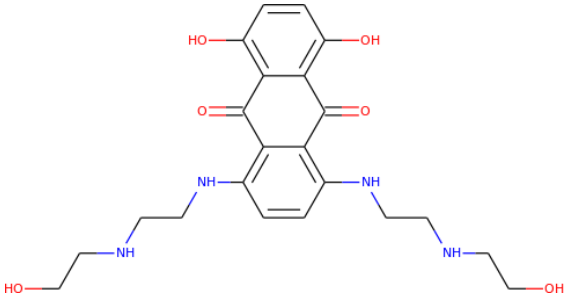
Materials and Methods

Molecular Docking

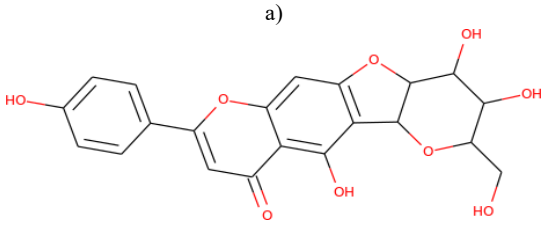
The ligand (chafuroside A, **Figure 2a**) was selected based upon the DNA genotoxicity activity of its analog chafuroside B (Hasegawa *et al*., 2013; Ganea *et al*., 2024). ligand SDF file was downloaded from PubChem (CID: 11269948) database and docked to B-DNA dodecamer retrieved from PDB database (PDB ID: 1BNA). The receptor crystal structure has a resolution of 1.90 Å and an R-value of 0.178 (Drew *et al*., 1981; Petchesi *et al*., 2025). Docking process was performed using Patch Dock (Schneidman-Duhovny *et al*., 2005; Yılmazer & Altinok, 2024) and results refinement via Fire Dock webservers (Andrusier *et al*., 2007; Zar *et al*., 2024). The best pose of docking was depicted in 3D via UCSF Chimera software (Pettersen *et al*., 2004; Yu *et al*., 2025) and a 2D diagram utilizing protein ligand interaction profiler (PLIP) program (Adasme *et al*., 2021; Mickevičius *et al*., 2024).

ADMET Parameters

For detecting the pharmacokinetics and toxicity properties of the ligand, the pkCSM online tool (Pires *et al*., 2015; Dupont & Lefevre, 2024) was used. Docking and ADMET parameters of chafuroside A were compared to the reference DNA intercalator and groove binder mitoxantrone (Kreft *et al*., 2018; Jagsi *et al*., 2025) **(Figure 2b)**



a)



b)

Figure 2. Chemical structures of mitoxantrone (reference drug, a) and chafuroside A (b).

Molecular Dynamics Simulation

Molecular dynamics (MD) simulations of the two docked complexes (Mitoxantrone and Chafuroside A) were performed to infer the stability, flexibility, and H-bonding. MD simulation was performed via the recently developed server Visual Dynamics (http://visualdynamics.fiocruz.br/) (Vieira *et al*., 2023; Zhang *et al*., 2023). The operating parameters were set as follows: water model (SPC), box type (triclinic), and box distance 0.35 mm. The force field employed was AMBER 03 for 100 ns. Root mean square deviation (RMSD), root mean square fluctuation (RMSF), and the number of H-bonds were plotted for the MD trajectories of the DNA-ligand complexes using Microsoft Excel ® 2019.

Results and Discussion

Docking Results

Apparently, from **Table 1**, chafuroside A exhibited high DNA binding energy mainly via VdW attraction. The binding free energy was higher than the reference drug mitoxantrone (-57.90 of chafruoside A vs -43.49 kcal/mole for mitoxantrone). Also, the atomic contact energy (ACE) is higher for chafuroside A.

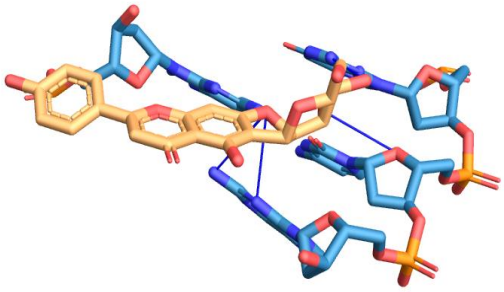
Table 1. PatchDock and FireDock results of the ligand and the reference drug mitoxantrone

Ligand	Patch Dock			Fire Dock				
	Score	Area	ACE	Global Energy	Attractive VdW	Repulsive VdW	ACE	HB
Chafuroside A	3798	463.30	-330.66	-57.90	-21.38	3.55	-19.58	0.00
Mitoxantrone	4378	542.20	-406.39	-43.49	-18.70	8.33	-17.95	0.00

ACE: atomic contact energy, HB: hydrogen bond, VdW: Van der Waals interaction. The unit of all parameters is in kcal/mol.

Regarding the binding mode of the ligand, chafuroside A was bound to the minor groove of DNA **(Figure 3a)**. It formed 2 conventional H-bonds with the DNA. This classifies chafuroside A to the minor groove binders group. The 2D diagram of the best pose revealed 3 H-bonds formed between DNA and ligand at distances of 1.93 and 2.21 Å **(Figure 3b)**. This reflects the strong interactions with DNA as needed to be genotoxic.

a)



b)

Figure 3. 3D and 2D interaction diagrams of the tested ligand to DNA. 3D diagram (a) proves the minor groove binding activity of the ligand (ligand shown in white). 2D diagram (b) illustrates the DNA-ligand interactions (DNA shown in blue, while ligand in light orange). Blue lines indicate the H-bonds.

ADMET Predictions

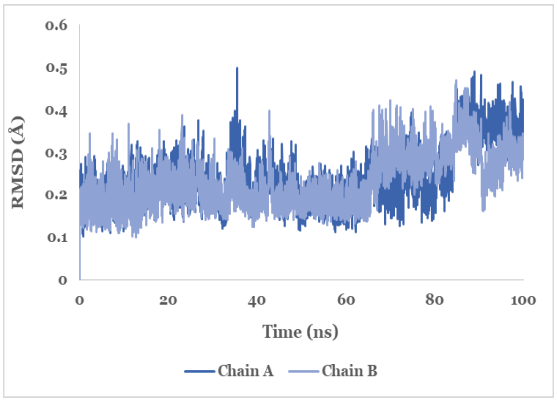
Table 2 summarizes the pharmacokinetic as well as the toxicity profiles of the ligand and reference drug. Chafuroside A fits well with Lipinski's rule of five, while mitoxantrone exhibited 1 violation. Furthermore, the absorption of chafuroside A from the gastrointestinal tract is about 2-fold higher than that of mitoxantrone. With respect to toxicity issues, chafuroside A is much safer in terms of maximum tolerated dose and hepatotoxicity. The two compounds are not carcinogenic based on AMES test. Overall, chafuroside A is better than mitoxantrone in DNA-binding energy or ADMET characteristics.

Table 2. ADMET parameters of the tested ligand compared to mitoxantrone.

Descriptor	Mitoxantrone	Chafuroside A
Molecular Weight	444.488	414.366
LogP	-0.1392	0.7862
#Rotatable Bonds	12	2
#H-Acceptors	10	9
#H-Donors	8	5
Surface Area	184.832	168.513
Lipinski's compatibility	1 violation	Accepted
Intestinal absorption%	31.681	65.821
Max. tolerated dose (log mg/kg/day)	0.689	0.385
Hepatotoxicity	Yes	No
AMES toxicity	No	No

MD Simulation

The two docked complexes were subjected to MD simulation to infer the stability, flexibility, and the formation of H-bonds during the overall course of MD simulation. The DNA strands of the PDB file (1BNA) are present as separate chains (A and B). The first MD output is RMSD, an index of the backbone deviation (stability) of the docked complex. It turned out that both chains exhibited more DNA strands backbone deviation when simulated for 100 ns upon binding to Mitoxantrone **(Figure 4a)** when compared to Chafuroside A **(Figure 4b)**. This was reflected by the corresponding RMSD values (from 0.1-0.4 Å) for DNA-Mitoxantrone and DNA-Chafuroside A (0.12-0.35), indicating a more stable profile of Chafuroside A. RMSF, on the flip side, is a measure of the stability of the individual DNA nucleotides upon binding the ligand. We found that DNA-Chafuroside A displayed fewer fluctuations in the nucleotides of both DNA strands in comparison with control DNA-Mitoxantrone. This was evident by the lower RMSF values of both complexes **(Figure 4c)**. The last parameter of the MD simulation was the formation of H-bonds. Although mitoxantrone formed a higher number of H-bonds throughout the whole course of MD simulation (100 ns) than Chafuroside A, the process was sporadic, i.e., the H-formed bonds were not evenly distributed throughout the MD simulation course (100 ns), in contrast to DNA-Chafuroside A, which exhibited fewer H-bonds but consistently as provided in **Figure 4d**.



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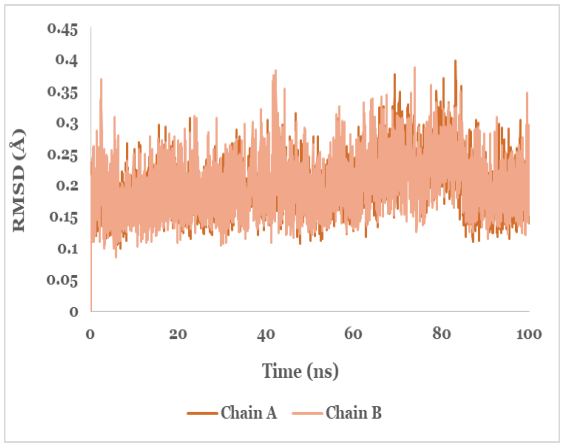

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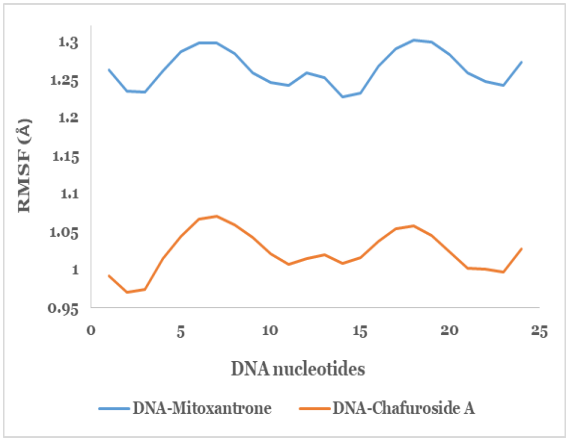

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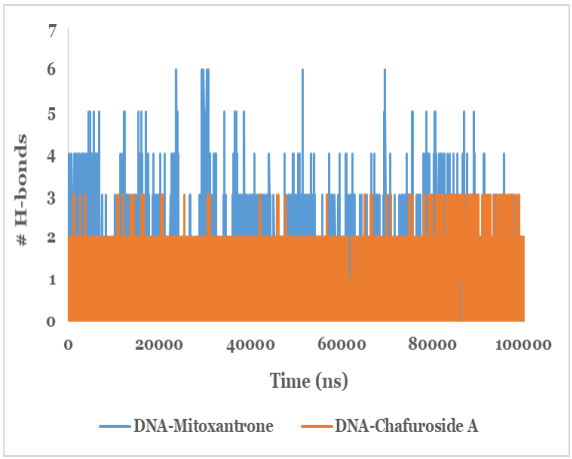

d)

Figure 4. MD simulation profile of DNA-Mitoxantrone complex and DNA-Chafuroside A complex

Cancer is a complex and dynamic disease that challenges the efforts of researchers to find effective treatments. Despite the continuous testing of various anti-tumor compounds, both natural and synthetic, cancer cells exhibit unique behaviors and adaptations that are hard to predict and overcome (Gatenby & Brown, 2020; Elamin *et al*., 2023; Kowalski *et al*., 2024; Pardo-Zamora & Castellano-Rioja, 2024). Therefore, it is important to explore new compounds that can target and disrupt the DNA of cancer cells, which is essential for their survival and proliferation. One such compound is chafuroside A, a natural glycoside that has been isolated from oolong tea and has shown anti-inflammatory and anti-diabetic properties (Weerawatanakorn *et al*., 2015; Maslyakova *et al*., 2023; Salem *et al*., 2025). In this study, we aim to evaluate the potential of chafuroside A as an anti-tumor agent by investigating its interaction and stability with DNA using computational methods. We also aim to predict its pharmacokinetic and toxicological characteristics using in silico tools. By doing so, we hope to provide new insights into the molecular mechanisms of chafuroside A and its suitability for further experimental validation.

The oolong tea is famous for its anti-cancer bioactivity. The underlying mechanism involves triggering DNA damage and cleavage at least against breast cancer (Shi *et al*., 2018; Leadbeatter & Tjaya, 2024). The main constituents accounting for this bioactivity are Chafuroside A and B. In the present study, we elucidated the mechanism by which Chafuroside A can block tumorigenesis progression as a minor-groove binder that will eventually result in the damage as well as cleavage of DNA. Indeed, Chafuroside A exhibited stronger binding to DNA as well as more stability than the control drug, as discovered through the molecular docking and MD simulation. Upon comparison with the control drug Mitoxantrone, Chafuroside A displayed a perfect druglikeness with no violations of Lipinski's rule of five. This puts another advantage to it, given that about 15% of drugs' FDA approval failure is attributed to druglikeness issues (Sun *et al*., 2022; Al-Mubarak *et al*., 2024; Bona *et al*., 2025). The third merit of Chafuroside over Mitoxantrone is that it is a natural product and can be administered routinely as a component of oolong tea. Altogether, this prioritizes Chafuroside A over mitoxantrone as a potential anti-tumor agent, which deserves wet-lab validation.

Conclusion

According to the docking, MD, and ADMET analysis, it can be concluded that the natural glycoside chafuroside A exhibited higher global binding energy and more stability than the reference drug mitoxantrone. The ligand binds to DNA in the minor groove. Also, chafuroside A had better pharmacokinetic characteristics with no toxicity issues when compared to the control drug mitoxantrone. In conclusion, chafuroside A is an extraordinary genotoxic drug candidate that needs to be validated by *in vitro* and *in vivo* experiments.

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Ethics statement: None

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