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Molecular Docking of Fenticonazole: Unveiling Its Therapeutic Potential in Breast and Lung Cancer

Dr. Sumitha A[1], Dr. Jesu Magdalene S[2], Dr. Samiya Begum Ibrahim[3], Dr. Dhivya L.S.[4]

[1]Associate Professor of Pharmacology, ACS medical college and Hospital, Dr. MGR Educational and research Institute, Chennai, Tamil Nadu, India – 600095. ORCID ID 0000- 0002-4537-7798
[2]Assistant Professor of Pathology, ACS medical college and Hospital, Dr. MGR Educational and research Institute, Chennai, Tamil Nadu, India – 600095. ORCID ID 0009-0007-3659-4815
[3]Associate Professor of Biochemistry, ACS medical college and Hospital, Dr. MGR Educational and research Institute, Chennai, Tamil Nadu, India – 600095. ORCID ID 0000-0003-2537-2647
[4]Assistant Professor of Pharmaceutical chemistry, Faculty of Pharmacy, Dr. MGR Educational and research Institute, Chennai, Tamil Nadu, India – 600095. ORCID ID 0000-0002-0517-5390.

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Corresponding Author:

Dr. Sumitha A
Associate Professor of Pharmacology, ACS medical college and Hospital, Dr. MGR Educational and research Institute, Chennai, Tamil Nadu, India – 600095. ORCID ID 0000- 0002-4537-7798
Email - arum.sumithadr@gmail.com

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ABSTRACT

In India, lung cancer is one of the leading cancers in terms of both incidence and mortality, while breast cancer is the most frequently diagnosed cancer among women. Repurposing of drugs has been done for its anticancer activity by molecular docking studies. Fenticonazole, antifungal drug belonging to imidazole group, was selected as the ligand for molecular docking analysis against Estrogen receptor and the CCND1-CDK4-P21 complex for Breast cancer and Lung cancer respectively in this study. Docking simulations were performed using AutoDock software (UCSF-Chimera©, version 1.5.7. Fenticonazole exhibits significant binding affinity with the Estrogen receptor (−12.5 kcal/mol) and the CCND1-CDK4-P21 complex (−11.8 kcal/mol). Docking of Fenticonazole with the Estrogen receptor revealed the formation of hydrogen bonds (LEU 384, ARG 394), van der Waals interactions (LEU 349, GLU 353, LEU 387, MET 528, PHE 404) and alkyl interactions (LEU 525). For the CCND1-CDK4-P21 complex, Fenticonazole formed hydrogen bonds (VAL 77, PHE 78) and van der Waals interactions (LEU 65, LEU 188, GLU 75, CYS 68, CYS 73). The research findings of this study pave the way for further experimental validation and in vivo studies to establish Fenticonazole's efficacy and safety in cancer treatment.

Keywords*: Fenticonazole, Docking, Lung cancer, Breast cancer.*

INTRODUCTION

India witnessed over 1.41 million new cancer cases and more than 910,000 deaths in 2022 due to cancer. Lung cancer stood out as the most prevalent cancer globally, representing 12.4% of new cases.[1,2] Lung cancer remained the primary contributor to cancer-related mortality, representing 18.7% of deaths, approximately 1.8 million deaths.3 Breast cancer ranked as the second most common cancer, comprising 11.6% of new cases, totaling 2.3 million cases. Breast cancer ranked as the fourth leading cause of cancer death, accounting for 6.9% of mortality.4

Many Anticancer drugs are currently in the market for treating lung cancer and Breast cancer. Still there is need of anticancer drugs with less adverse effects. Repurposing of drugs with other pharmacological actions has been done for its anticancer activity.5,6,7 By molecular docking method, existing drugs against new targets can identify potential new uses for approved drugs.. Molecular docking studies are an essential method in contemporary drug design for analyzing drug-

receptor interactions. Docking can predict interactions in multi-target drug designs, such as combination therapies for cancer or other complex diseases.8

Molecular docking is a powerful computational technique that enables the virtual screening of thousands or even millions of compounds against cancer-related target proteins. This approach is widely employed in modern drug discovery due to its efficiency and cost-effectiveness compared to experimental screening methods.9 Molecular docking methods screen for anticancer agents, predicting binding affinities and elucidating the molecular interactions between ligands and biological receptors.10

Many antifungal drugs has shown anticancer activity in their invitro studies.11 However, emerging research has revealed their potential as anticancer agents, attributed to multiple mechanisms. One key mechanism is their inhibitory activity against P-glycoprotein (P-gp), a membrane transporter often overexpressed in multidrug-resistant cancer cells. P-gp actively pumps chemotherapeutic agents out of cells, reducing drug accumulation and efficacy.

By inhibiting P-gp, azole antifungals can sensitize resistant cancer cells to chemotherapy, enhancing cytotoxic effects.12These medications incorporate either an imidazole or triazole ring, capable of reversing chemoresistance and thereby suppressing angiogenesis and regulates signaling pathways within cancer cells.13 Top of Form

Fenticonazole is an antifungal drug that belongs to imidazole derivative. Fenticonazole inhibits fungal CYP450 isozyme lanosterol 14-alpha-demethylase and impairs fungal ergosterol synthesis. The ergosterol synthesis is hindered, which results in leaky fungal cell membrane.14,15 Fenticonazole's ability also to inhibit the secretion of protease by Candida albicans is significant in combating fungal infections.16

In previous studies, Fenticonazole prevent estrogen receptor transcriptional signaling and anti proliferative activity in cancer cell modelling studies of Breast cancer.17 In this study, an attempt to evaluate anticancer activity of Fenticonazole against lung cancer and Breast cancer by Molecular docking method is being tried.

MATERIALS AND METHODS:

Ligand Selection:

In this study, Fenticonazole was selected as the ligand for molecular docking analysis against Breast and lung cancer. The three-dimensional (3D) structure of the ligand, in Simple Data Format (SDF), was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/compound; last accessed on December 21, 2025).

Receptor/Protein Preparation:

The preparation of target proteins followed the protocol outlined by Meng et al.18. The target proteins for Breast cancer and Lung cancer selected were Estrogen receptor and CCND1-CDK4-P21 complex respectively. The structures of the Estrogen receptor (PDB ID: 3ERT) and CCND1-CDK4-P21 complex (PDB ID: 6P8H) were retrieved from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/. Ligands were prepared in AutoDock by uploading the SDF files to the input server. Docking simulations were performed using AutoDock software (UCSF-Chimera©, version 1.5.7. After selection as docking molecules- charges, hydrogen atoms, and torsion angles were added to the ligand molecules. The prepared ligands were saved in PDBQT format for subsequent analysis. The protein structures were prepared by removing water molecules, adding polar hydrogen atoms, and calculating Gasteiger charges. The processed protein files were then saved in PDBQT format and used for the docking procedure.The grid size was set to 90 × 90 × 90 points (x, y, z) with a spacing of 0.375 Å. The grid center was defined by the coordinates x = 8.333, y = −11.151, z = −31.135 Å. Both the ligand and protein were treated as rigid entities during the docking process. AutoDock utilized the prepared ligand and protein files, along with grid box parameters specified in a configuration file, for docking simulations. Upon completion, AutoDock generated 25 docking configurations for each protein-ligand complex. The docking pose with the lowest binding energy (in kcal/mol) and minimum root mean square deviation (RMSD) was identified as the optimal configuration. The resulting protein-ligand complexes were visualized and analyzed using Discovery Studio software (version 2.4.1, 2016). This enabled a detailed examination of molecular interactions and docking poses.19,20

RESULTS

Fenticonazole demonstrated the highest binding affinity score of −12.5 kcal/mol with the Estrogen receptor compared to the reference standard Paclitaxel, which showed a binding affinity of −7.18 kcal/mol. For the CCND1-CDK4-P21 complex, Fenticonazole exhibited a binding affinity of −11.8 kcal/mol, while Paclitaxel had a score of −7.73 kcal/mol as shown in Table 1.

Table 1. Docking Analysis of Fenticonazole against Targeted Proteins

S.No.	Compounds	Binding Affinity PDB ID:3ERT (-Kcal/mol)	Binding Affinity PDB ID:6P8H (-Kcal/mol)
01.	Fenticonazole	−12.5	−11.8

02.	Paclitaxel	-7.18	-7.73

Docking of Fenticonazole with the Estrogen receptor revealed the formation of hydrogen bonds (LEU 384, ARG 394), van der Waals interactions (LEU 349, GLU 353, LEU 387, MET 528, PHE 404) and alkyl interactions (LEU 525). In comparison, the docking of Paclitaxel with the Estrogen receptor formed hydrogen bonds (ARG 394), van der Waals interactions (GLU 353, LEU 487, MET 528, PHE 404) and alkyl interactions (PRO 607).

For the CCND1-CDK4-P21 complex, Fenticonazole formed hydrogen bonds (VAL 77, PHE 78) and van der Waals interactions (LEU 65, LEU 188, GLU 75, CYS 68, CYS 73). Paclitaxel docking with the CCND1-CDK4-P21 complex showed hydrogen bonds (GLY 62, VAL 37) and van der Waals interactions (LEU 65, GLU 75, PRO 60, THR 66).In Figures 1 and 2, the following color-coded representations are used: green balls and sticks depict hydrogen bonds, violet balls and sticks represent hydrophobic bonds (Pi-Pi/Pi-sigma/amide-Pi interactions), pink balls and sticks illustrate hydrophobic interactions (Pi-alkyl/alkyl interaction stacking), gold balls and sticks show hydrophobic bonds (Pi-sulfur), and white balls and sticks represent carbon-hydrogen bonds.

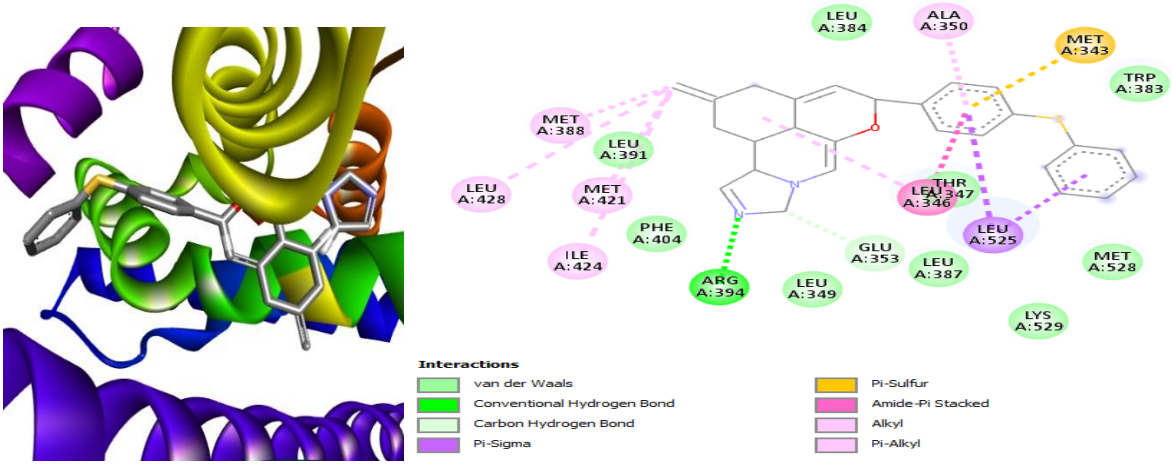

Figure 1: 2D and 3D Visualization of Fenticonazole against Estrogen Receptor

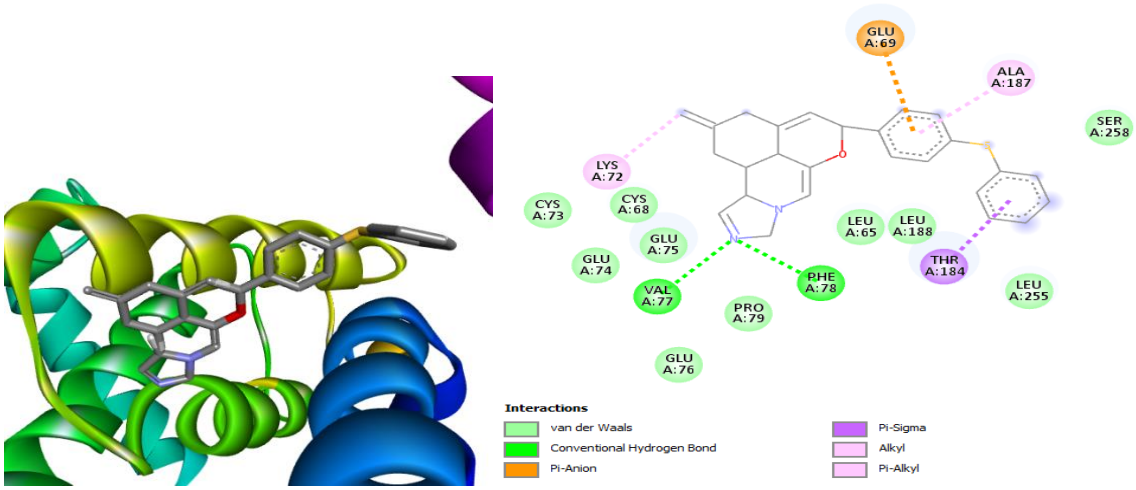

Figure 2: 2D and 3D Visualization of Fenticonazole against CCND1-CDK4-P21 complex

DISCUSSION

The present investigation provides compelling evidence supporting the potential repurposing of Fenticonazole, an imidazole-class antifungal agent, as a promising anticancer candidate against breast and lung cancers. Drug repurposing has emerged as a strategic approach in oncology to accelerate drug development while minimizing cost and safety concerns, particularly for compounds with well-established pharmacokinetic and toxicity profiles.21 The current molecular docking analysis offers valuable insights into the interaction of Fenticonazole with key molecular targets involved in tumor progression.

The docking results revealed that Fenticonazole exhibits remarkably high binding affinity toward the estrogen receptor (ER) (−12.5 kcal/mol) and the CCND1-CDK4-P21 complex (−11.8 kcal/mol), significantly outperforming the standard chemotherapeutic agent paclitaxel. Binding affinity is a critical parameter reflecting the stability of ligand–receptor

complexes, and values lower than −10 kcal/mol are generally indicative of strong and biologically relevant interactions. The superior binding profile observed in this study suggests that Fenticonazole may effectively inhibit these targets, thereby exerting anticancer effects.

At the molecular level, Fenticonazole demonstrated multiple stabilizing interactions, including hydrogen bonding, van der Waals forces, and hydrophobic interactions. In the estrogen receptor complex, key hydrogen bonds with LEU 384 and ARG 394, along with extensive hydrophobic contacts (LEU 349, GLU 353, MET 528, and PHE 404), indicate a strong and stable binding within the ligand-binding domain. These residues are known to play a crucial role in ligand recognition and receptor activation, as reported in structural studies of ER-ligand complexes. The interaction pattern suggests that Fenticonazole may act as an estrogen receptor modulator or antagonist, thereby inhibiting estrogen-driven proliferation in breast cancer cells. Similarly, in the CCND1-CDK4-P21 complex, which is a critical regulator of cell cycle progression, Fenticonazole formed hydrogen bonds with VAL 77 and PHE 78, along with significant van der Waals interactions involving residues such as LEU 65, GLU 75, and CYS 68. The Cyclin D1-CDK4 complex plays a pivotal role in the G1 to S phase transition, and its dysregulation is frequently associated with uncontrolled cell proliferation in cancers, particularly lung cancer. Inhibition of this complex can lead to cell cycle arrest, a well-established anticancer mechanism. Therefore, the observed binding interactions suggest that Fenticonazole may interfere with cell cycle progression, contributing to its anticancer potential.

Fenticonazole, in particular, has been previously reported to exhibit anti-estrogenic activity by suppressing estrogen receptor-mediated transcriptional signaling in breast cancer models.22 This aligns well with the current docking results, reinforcing the hypothesis that Fenticonazole may function as a targeted therapeutic agent in hormone-dependent cancers. Moreover, its ability to disrupt fungal cytochrome P450 enzymes suggests a potential to interfere with similar enzymatic pathways in cancer cells, thereby contributing to anticancer effects.23

Another important aspect of this study is the comparison with Paclitaxel, a widely used chemotherapeutic drug. Although Paclitaxel is effective, it is associated with significant adverse effects and resistance issues. The higher binding affinity of Fenticonazole observed in this study indicates that it may serve as a safer and more effective alternative, particularly in cases where resistance to conventional chemotherapy develops. Furthermore, the multi-target binding capability of Fenticonazole supports its potential use in combination therapy, which is increasingly recognized as an effective strategy to combat cancer heterogeneity and drug resistance. Despite these promising findings, it is important to acknowledge the limitations of the study. Molecular docking provides a predictive model of ligand–receptor interactions but does not account for the dynamic nature of biological systems. Factors such as protein flexibility, solvent effects, and cellular context are not fully represented.

CONCLUSION

The research findings of this study pave the way for further experimental validation and in vivo studies to establish Fenticonazole's efficacy and safety in cancer treatment. By leveraging drug repurposing strategies, Fenticonazole could offer a promising alternative for managing lung and breast cancers, particularly in addressing challenges such as drug resistance and minimizing adverse effects associated with conventional therapies

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Conflict of Interest

None

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