



3D Drug Docking of Eugenol and Cyclophosphamide against the Protein of Abl1 (Leukemia) Using Insilico Methods.

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ABSTRACT

Background: To use insilico techniques to examine the potential effectiveness of Eugenol against the Tyrosine-protein kinase ABL1 Antigenic peptide (Model Archive: <https://modelarchive.org/doi/10.5452/ma-kher5>). Our current work's main objective is to dock the modeled ABL1 peptide (Leukemia) with eugenol, a bioactive substance obtained from the Tulsi plant (*Ocimum tenuiflorum*). Eugenol's effectiveness against the ABL1 peptide was predicted using drug docking studies.

Materials and procedures: The genomic sequence of ABL1-Peptide was obtained from the UniProt database and docked with cyclophosphamide, a control agent, and eugenol, a bioactive drug already in use, using the CBDOCK server.

Findings and Conversation: The current investigation shows that cyclophosphamide, the reference drug, interacts effectively with ABL1-peptide. The effectiveness of the drug against the leukemia-causing protein was evaluated using the docking score. Eugenol has a greater binding affinity than the control drug cyclophosphamide. Therefore, eugenol may be a good option when combined with the anti-cancer activity protein ABL1 in leukemia. The study concludes that anti-cancer drugs effectively block ABL1. The field of contemporary cancer informatics research is significantly impacted by the findings of this study.

Keywords: Tyrosine-protein kinase ABL1, *Eugenol*, Cyclophosphamide (reference medication), Model Archive, (CBDOCK, and Discovery Studio).

1.0 INTRODUCTION

The widely expressed nonreceptor tyrosine kinase ABL1 is significantly impacted by subcellular location and posttranslational modifications [1-3]. Cell survival and proliferation are enhanced by ABL1 expression in the cytoplasm. In reaction to genotoxic stress, ABL1 is translocated into the nucleus and/or mitochondria, where its activity regulates DNA repair, triggers apoptosis/necrosis, and prevents cell growth. Hematopoietic stem cells (HSCs) and the myeloid compartment do not require proper ABL1 kinase activity, but B and T cell development must [4-6]. Constitutively activated oncogenic mutations of the ABL1 tyrosine kinase have a major impact on the pathophysiology of both acute and chronic leukemias. Usually, chromosomal translocations (BCR-ABL1, TEL-ABL1, and others) or episomal amplification (NUP214-ABL1) cause activation. The BCR-ABL1 fusion oncogene, which results from t(9;22)(q34;q11), is present in all patients with chronic myeloid leukemia (CML), approximately 25% of pre-B acute lymphocytic leukemia (ALL), and infrequently de novo acute myeloid leukemia (AML).⁷ Only when BCR-ABL1 kinase is expressed in an HSC with the capacity to self-renew, transforming it into a leukemia stem cell (LSC), can it become leukemogenic [8].

During the CML–chronic phase (CML–CP), LSCs can produce large amounts of leukemia common myeloid (LCMPs) and leukemia granulocyte/macrophage (LGMPs), two types of leukemia early progenitor cells (LPCs) that are unable to self-renew and eventually grow into mature cells. Consequently, CML–CP is a progenitor-driven illness that began with stem cells.⁸ The shift from a relatively benign CML–CP to the aggressive and lethal blast phase (CML–blast phase [CML–BP]) is associated with expansion of LSCs, enhanced proliferation, delayed differentiation, drug resistance, and the accumulation of further genetic and epigenetic defects [9, 10]. NUP214-ABL1 fusion is the product of extrachromosomal (episomal) amplification after the 500-kb genomic stretch from ABL1 to NUP214 is circularized [11].

The NUP214-ABL1 gene is present in about 4% of adult ALL patients. Additional ABL1 fusion genes have been discovered, despite their rarity. For example, the ETV6(TEL)-ABL1 fusion gene, which results from a t(9;12)(q34;p13), may occasionally be present in patients with acute leukemias or myeloproliferative disorders. EML1, ZMIZ1, and RCSD1 were identified as ABL1 partners in ALLs.

Due to its crucial role in controlling cell motility, adhesion, autophagy, DNA damage response, apoptosis, and proliferation, leukemias that express oncogenic variants of the ABL1 kinase also frequently have the nonmutated allele that encodes the standard ABL1 kinase, which could have a substantial impact on the disease's pathogenesis and/or treatment response [1-3]. This theory is supported by previous research showing that as chronic myeloid

leukemia advances from chronic phase (CML-CP) to blast phase (CML-BP), normal ABL1 expression is lost due to interstitial deletion on chromosome 9 [del(9q34)] and/or transcriptional repression of the alternative ABL1 promoter linked to BCR-ABL1 translocation.^{12,13} Crucially, BCR-ABL1 cells showed reduced sensitivity to tyrosine kinase inhibitors (TKIs) such as imatinib when ABL1 was absent [14].

2.0 MATERIALS AND METHODS

Ligand selection: Chemical compounds having NSAID (nonsteroidal anti-inflammatory medication) properties, such as eugenol and cyclophosphamide (control drug), were the focus of a molecular docking investigation. PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) provided the simplified molecular input line entry system (SMILES) format for the chosen substances [18]. To obtain the PDB structure, the three chemical compounds' canonical SMILES (Simplified Molecular Input Line Entry System) were sent to the Online SMILES Translator (<https://cactus.nci.nih.gov/translate/>). To conduct pharmacological docking studies, the 3D antigenic Leukemia peptide was acquired from the PDB-Model repository (<https://modelarchive.org/doi/10.5452/ma-kher5>).

Drug Docking: Molecular drug docking, which looks at tiny molecules' ideal conformations during interactions with target molecules, is one of the most popular *insilico* drug discovery techniques. Docking analyses were performed on ABL1 and two chemical compounds. To predict the interaction between receptor and ligand molecules, PDB data for the ligand and receptor 3D structures were uploaded to the CBDOCK website [19] (<http://hdock.phys.hust.edu.cn/>). The surface residues of the ligand and receptor were also disclosed by the CBDOCK investigation.

3D macromolecular visualization: Two compounds, ketorolac tromethamine and cyclophosphamide, a control medication, were subjected to molecular drug docking investigations using ABL1. Discovery Studio, a molecular visualization program, was used to display the compounds' three-dimensional structures.

3.0 RESULTS AND DISCUSSION

Compounds like the test chemical *Eugenol* and the control drug are used to assess the binding efficacy. Table 1 displays the docking of cyclophosphamide with the modelled ABL1. Out of the top 10 binding models produced by the CBDOCK server, the binding model with the highest docking score (Table 1) was selected due to its higher binding affinity for the receptor. The control medication, *Cyclophosphamide*, has a docking score of -5.4 kcal/mol and -6.4 kcal/mol, respectively, whereas the *Eugenol* molecule has a stronger binding affinity with a docking value of -6.4 kcal/mol.

The score represents the possible energy change that might arise from the ligand-protein interaction. Thus, a very negative score indicates a strong link, while a less negative or positive value indicates a weak or absent bond. Using CBDOCK, a cutting-edge online server for template-based modeling and free docking, eugenol and cyclophosphamide (as the control medication) were docked with the modeled Leukemia 1 (ABL1) Peptide in this study. The drug binding affinities of the ligand and receptor are displayed in Table 1.

The three-dimensional (3D) structure of the ligand and receptor was analyzed using the molecular visualization application Discovery Studio after the docking analysis, as seen in Figures 1-5 for the control medication cyclophosphamide and (ABL1) and Figures 6-9 for eugenol and (ABL1). The effectiveness of the CBDOCK server has been demonstrated by earlier research.

Table 1: Summary of docking scores of ligand and receptor

Receptor	Drug	Docking Score
Tyrosine-protein kinase ABL1	Cyclophosphamide (control drug)	-5.4 kcal/mol
Tyrosine-protein kinase ABL1	Eugenol	-6.4 kcal/mol

Note: According to the docking score above, *Eugenol* most successfully inhibits the growth of *Leukemia* protein cells for ABL1. The most successful treatment for *Leukemia* is *Cyclophosphamide*, the control drug.

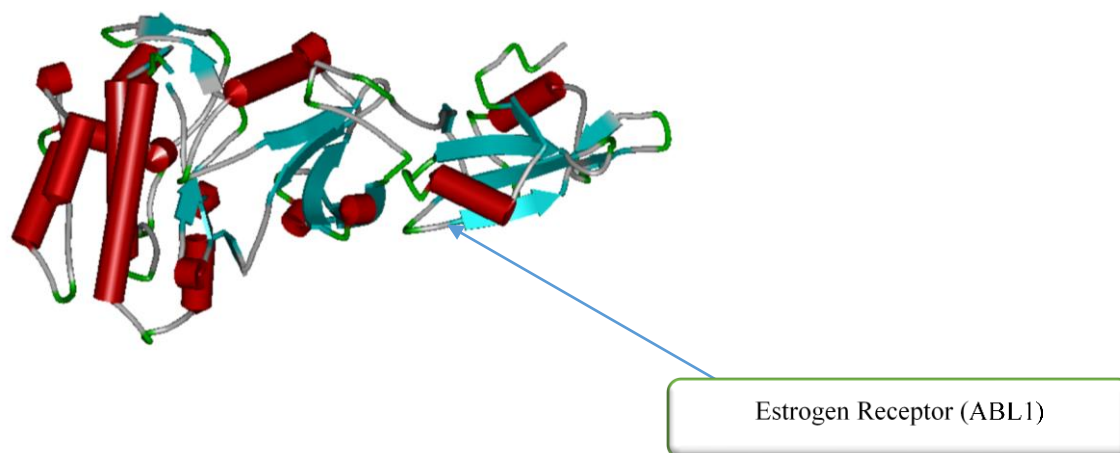


Figure 1: Schematic model view of *Leukemia* (ABL1) viewed with visualization tool, Discovery Studio.

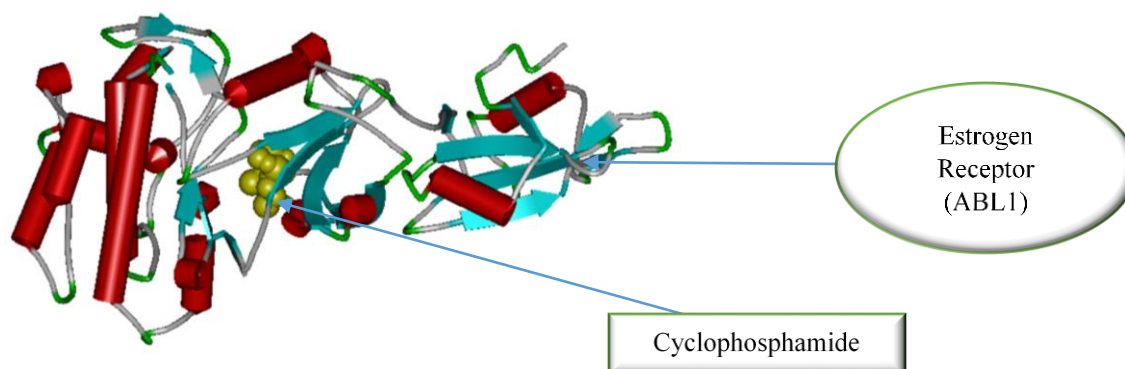


Figure 2: Schematic model view of *Cyclophosphamide* and *Leukemia* (ABL1) (3D Complex) viewed with visualization tool, Discovery Studio.

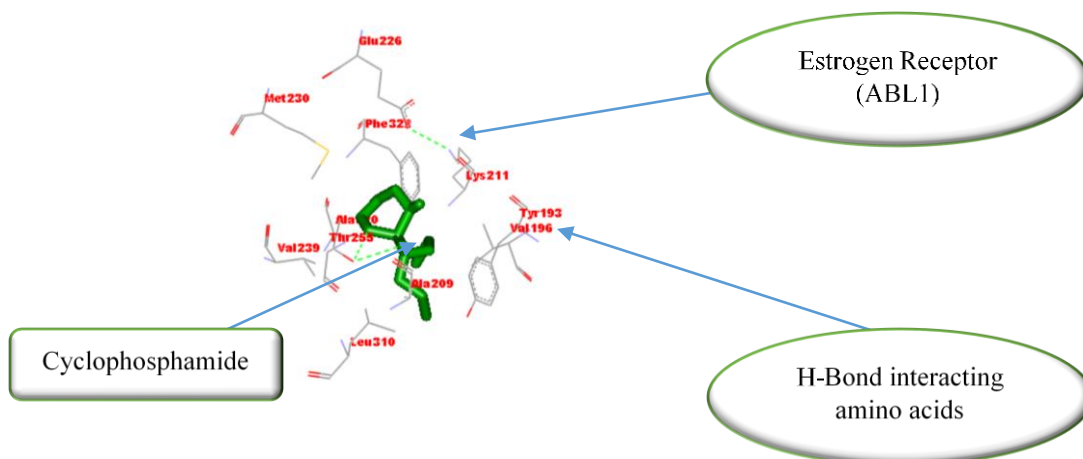


Figure 3: H-Bond interactions model view of *Cyclophosphamide* and *Leukemia* (ABL1) viewed with visualization tool, Discovery Studio.

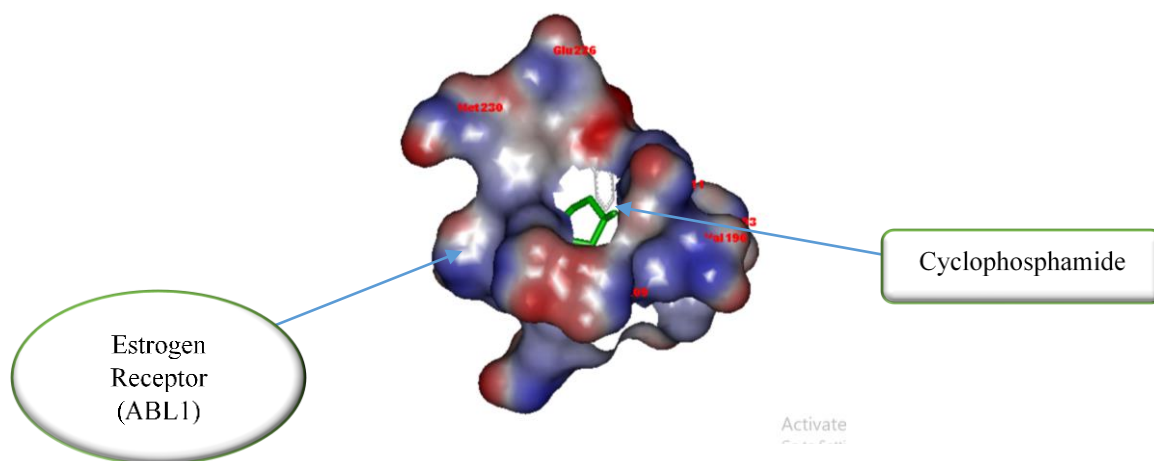


Figure 4: Van der Waals interactions model view of *Cyclophosphamide* and *Leukemia* (ABL1) viewed with visualization tool, Discovery Studio.

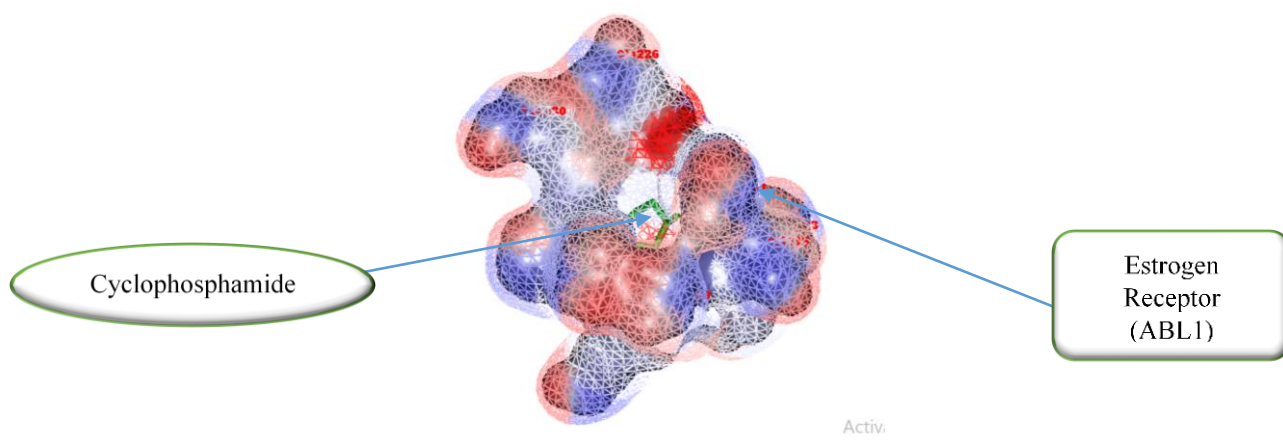


Figure 5: Electrostatics force model view of *Cyclophosphamide* and *Leukemia* (ABL1) and *Leukemia* (ABL1) viewed with the visualization tool, Discovery Studio.

Drug and protein complex: A drug is essentially a highly tailored, custom-made key or a pair of molecular handcuffs sent into the city. The drug and the corresponding protein work well together. This combination structure is known as the drug-protein complex. **Drug and receptor electrostatic force:** The strong, non-covalent attraction that occurs when a positively charged region on a drug molecule aligns with a negatively charged region on a receptor protein is known as the electrostatic force between a receptor and a drug. Imagine your medicine molecule as the matching key and your receptor protein as a safe electronic door lock.

Electrostatic forces act as natural magnets that pull the drug-key toward the keyhole from a distance, even though some parts of the key must match the geometry of the lock. On the other hand, an intelligent drug designer will give the drug molecule a consistent positive charge at the exact spot if your target protein contains a section of amino acids that carry a negative charge (like Glu or Asp). These magnetic forces provide an extensive attraction when the drug passes through the crowded cellular environment. They create a stable drug-protein combination that either deactivates or activates the target by inserting the drug straight into the binding site and securing it firmly.

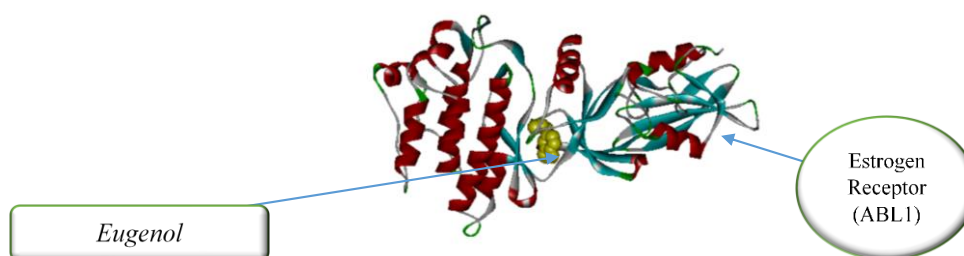


Figure 6: Tube model view of *Eugenol* and *Leukemia* (ABL1) viewed with the visualization tool Discovery Studio.

The docking study enables the evaluation, screening, and prediction of the computational electrostatics of the ligand-receptor complex [21], according to Sahoo et al. [20]. According to Mohapatra et al., this inquiry typically comprises of two separate steps [22]. Initially, the active site of the protein is used to sample ligand conformations. Second, a scoring system is used to rank conformations. Dash et al. [23] state that sampling algorithms should theoretically replicate experimental binding modes and that a scoring system should be used to assess confirmations [24].

According to Sahoo et al. [25] and Pramanik et al. [26], the dry lab approach has a major benefit over in vivo lab investigations in terms of resource and time commitment. According to Nanda et al. [27], this method forecasts the orientation of the ligand in a complex that the ligand forms with proteins or enzymes. Additionally, the interaction is quantified by the geometry and electrostatic interaction of the docked complex.

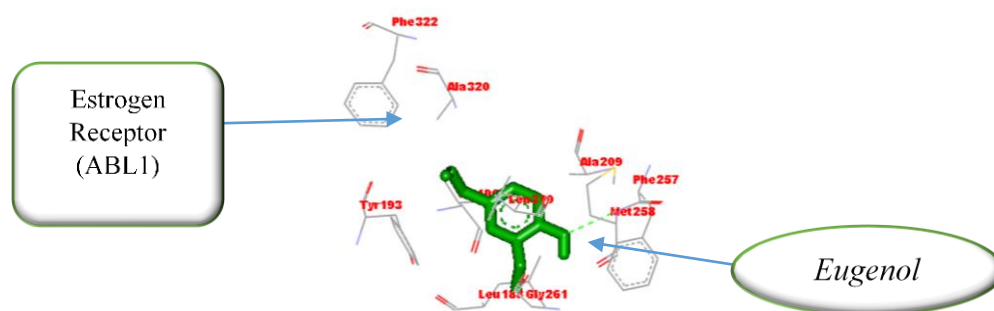


Figure 7: H-Bond interactions model view of *Eugenol* and Leukemia (ABL1) viewed with visualization tool, Discovery Studio.

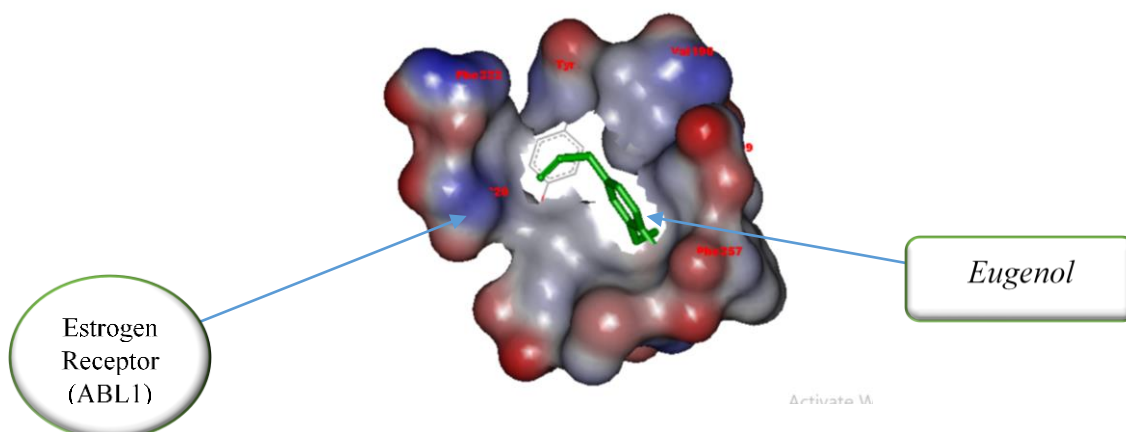


Figure 8: Van der Waals interactions model view of *Eugenol* and Leukemia (ABL1) viewed with visualization tool, Discovery Studio.

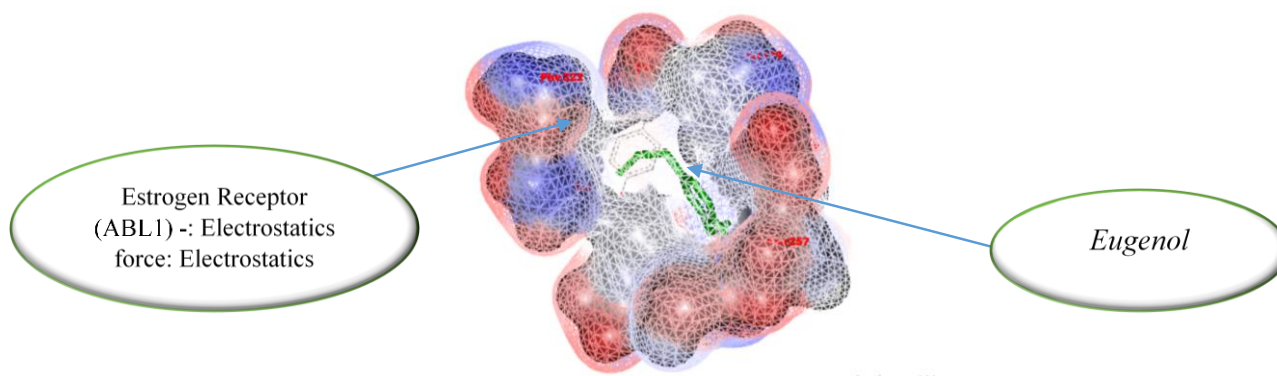


Figure 9: Electrostatics force model view of *Eugenol* and Leukemia (ABL1) and Leukemia (ABL1) viewed with the visualization tool, Discovery Studio.

Drug-receptor Van der Waals interaction: Van der Waals forces are weak, short-range electrostatic attractions that occur when the electron clouds of two neutral atoms get closer to one another. As a result, the atoms are softly pulled together by transitory dipoles. If electrostatic interactions are comparable to strong magnets, Van der Waals forces can be compared to molecular Velcro. Consider a high-security lock (the receptor protein) and a key (the drug molecule). The magnets (electrostatic forces) can draw the key to the lock from a distance, but the key must precisely fit the internal geometry of the lock to turn it.

Drug docking mechanisms: ABL1 mutations alone do not fully explain endocrine resistance in MBC. About 50% of cases of endocrine resistance are associated with an ABL1 mutation; additional, increasingly identified reasons include ABL1 deletion, amplification, and translocation as well as modifications in the PI3K-AKT-mTORC1, RAS-MAPK, and CDK4/6-RB-E2F pathways [26]. Additionally, ABL1 mutations frequently occur with other concurrent genetic alterations, which together lead to a poorer prognosis globally [27, 28].

This study used virtual screening and molecular docking simulations to assess the binding kinetics of the common anti-inflammatory drug Eugenol and the Leukemia (ABL1) inhibitor cyclophosphamide, which acted as a reference control molecule. Eugenol is the primary bioactive component of the Tulsi plant (*Ocimum sanctum* or *Ocimum tenuiflorum*), also known as Holy Basil. Although clove oil is the most concentrated source of eugenol worldwide, tulsi relies on eugenol for its distinct, potent, clove-like aroma and its well-known medical properties.

Its competitive docking score was -6.4 kcal/mol. Strong steric compatibility with the hydrophobic and electrostatic residues in the target protein's functional domain is shown by eugenol's consistent interaction characteristics. LEU188 GLY189 GLN192 TYR193 VAL196 ALA209 VAL210 LYS211 GLU226 MET230 VAL239 ILE253 THR255 GLU256 PHE257 MET258 THR259 TYR260 GLY261 ASN262 ASP265 LEU310 ALA320 ASP321 PHE322 are the amino acids that interact with the H-Bond against the ABL1 modeled peptide.

Phosphorodiamide Cyclophosphamide is 1, 3, 2-oxazaphosphinan-2-amine 2-oxide in which the amino nitrogen atom has two 2-chloroethyl groups attached. Its activities include alkylating, antineoplastic, xenobiotic, immunosuppressive, antirheumatic, carcinogenic, environmental pollutant, and medication allergen. Cyclophosphamide attained a moderate docking affinity of -5.4 kcal/mol as a reference standard in this situation. An examination of the molecular dynamics and electrostatic interaction summaries revealed that all three ligand complexes had a well-conserved binding pocket.

Essential amino acid residues such as LEU188 TYR193 VAL196 ALA209 VAL210 LYS211 GLU226 MET230 VAL239 ILE253 ILE254 THR255 GLU256 PHE257 MET258 LEU310 ALA320 ASP321 PHE322 were consistently involved in the structural binding network for each control drug. The regular recruitment of these particular hydrophobic, neutral, and hydrophilic amino acid sites underscores their importance as critical hotspots for precise structural stabilization. The combined thermodynamic data suggests that these compounds bind to the key functional areas of the modeled *Leukemia* (ABL1) transporter. It is evident from the docking experiments that *Eugenol* is present at the membrane areas' binding site [29, 30].

4. CONCLUSION

One of the most prevalent malignancies that affect people is *leukemia*. It occurs when *leukemia* cells proliferate and develop into tumors. The findings unequivocally demonstrate that the medications (*Eugenol*, and the control medicine - *Cyclophosphamide*) may inhibit the hydrophobic parts of the unique anticipated structure of *leukemia 1* (ABL1). The Model Archive has received the modeled structure. According to this research, Eugenol, a bioactive compound and potential therapeutic agent derived from *Ocimum tenuiflorum*, binds to ABL1 effectively. The field of contemporary *leukemia*-specific cancer informatics research depends heavily on the findings of this study.

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6. CONFLICT OF INTEREST

No conflicts of interest are disclosed by the writers.

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