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Molecular Docking Analysis of Phytocompounds from *Ficus hispida* Against Epidermal Growth Factor Receptor Kinase Domain

Lavanya Burra*

Abstract

The Epidermal Growth Factor Receptor (EGFR) kinase domain plays a key role in cancer, as it promotes tumour growth and helps cancer cells survive, making it an important focus for developing treatments. Through comprehensive computational analysis, this study investigates the anticancer potential of phytocompounds from Ficus hispida, a medicinal plant renowned for its diverse bioactive compounds, as novel EGFR inhibitors. Molecular docking techniques using Py Rx software were employed to evaluate the binding interactions of 34 Ficus hispida phytocompounds against the EGFR Kinase domain (PDB ID: 2ITN). Swiss ADME analysis assessed. The top-performing compounds for drug-likeness and pharmacokinetic properties. Protein structure validation was conducted using Ramachandran plot analysis, and molecular interactions were visualized using BIOVIA Discovery Studio. Four phytocompounds demonstrated exceptional binding affinities: Isoderrone (–9.2 Kcal/mol), Ficuisoflavone (–9.1 Kcal/mol), Ficusin A (–8.9 Kcal/mol), and Hispidacine (–8.9 Kcal/mol). All compounds satisfied Lipinski's rule of five, exhibited favorable ADMET properties, and formed stable hydrogen bonds and hydrophobic interactions with key catalytic residues. The EGFR protein structure showed 85.1% residues in favourable regions, confirming structural reliability. Ficus hispida phytocompounds, particularly Ficusin A and Isoderrone, demonstrate significant potential as natural EGFR inhibitors with favourable pharmacokinetic profiles, warranting further experimental validation for anticancer drug development.

Keywords: *Ficus hispida*, EGFR kinase domain, molecular docking, molecular dynamics, ADME analysis, drug discovery, phytocompounds, cancer

INTRODUCTION

Ficus hispida is a member of the Moraceae family. It is a fascinating plant with significant ethnopharmacological uses [1]. It has peculiar shapes and occurs in numerous tropical regions. It has gained much scientific attention due to its intricate chemicals and multiple health applications [2]. *Ficus hispida*, or the rough-leaved figure, is a tropical plant that is renowned for its incredible healing properties in traditional medicine. This shrub or tree is native to Southeast Asia, India, and Australia. It can be found flourishing in many locations, such as riverbanks and thick forests. It is a valuable plant with its rough leaves, unusual fruits, and significant medicinal purposes that has been prized for centuries [3, 4].

Ficus hispida is extensively utilized in Ayurveda and traditional medicine. Various plant parts, such as leaves, roots, and fruits, are used to treat various ailments. They include skin infections and digestive diseases. One research area is investigating the

***Author for Correspondence**
Lavanya Burra
E-mail: Lavanyaburra4697@gmail.com

Student, Department of Bioinformatics, BioNome Private Limited, Bengaluru, Karnataka, India

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phytocompounds of *Ficus hispida*. These phytocompounds have the potential to inhibit the epidermal growth receptor kinase domain. This domain is a prime target in the development of anticancer drugs.

Ficus hispida possesses strong anticancer activity. It is primarily because of its dense composition of phytochemicals. It possesses numerous secondary metabolites, such as flavonoids, terpenoids, and phenolic compounds [5]. The plant is a significant element of traditional medicine. It is applied in numerous healing traditions. Various parts of the plant, roots, and fruits are used by indigenous groups for treating respiratory infections, skin diseases, and other ailments. This reflects their diverse healing capabilities [6].

The phytochemical analysis demonstrates that *Ficus hispida* contains numerous bioactive compounds. Most of these compounds exhibit antibacterial, anti-inflammatory, anti-cancer, and antioxidant activities [7]. Molecular analysis has gradually described how these phytocompounds alter cell signaling pathways. They also regulate immune responses [8].

The ability of the plant to hit significant molecular pathways has been showcased in recent pharma research [9]. *Ficus hispida* possesses phytocompounds that might interfere with neoplastic signaling pathways. This renders the Epidermal Growth Factor Receptor (EGFR) a critical target [10]. One of the sophisticated computational tools for understanding potential drug interactions is the Molecular Docking (M.D) method. Scientists can investigate the molecular characteristics of herbal drugs. They can investigate therapies by tracing connection mechanisms. They can also compute interaction affinities [11, 12].

Growth Factor Epidermal Receptors (GFER) are major targets in cancer therapy. They are involved in signal transduction, survival, and cell growth. The tyrosine kinase domain of the receptor also regulates intricate signal pathways within cells. When they are dysregulated, they give rise to various forms of cancer [13]. The development of small-molecule inhibitors that target specifically EGFR activity has hence been the focus of considerable attention [14]. Since most of the phytochemicals display inhibitory activities against the EGFR, natural products are being identified as an attractive source for new EGFR-targeting compounds [15].

Ficus hispida is a traditional medicine with a historical background. It is a good potential source of bioactive substances that could serve as therapeutic agents [16]. The plant is rich in a diverse composition of phytochemicals, such as flavonoids, phenolic acids, and alkaloids. This species yields a distinct array of molecules. Scientists can leverage this to find novel methods for cancer treatment [17]. This research employs molecular docking to study how some *Ficus hispida* phytochemicals interact with the EGFR kinase domain. The objective is to identify lead compounds to use in creating EGFR-targeted anticancer drugs.

The marriage of computational molecular methods and conventional medicinal plant research provides an alternative method of drug discovery [18]. Simulations of molecular docking facilitate the exploration of ligand-receptor interactions. This provides us with new perspectives regarding the curative potential of plant compounds [19]. In this research, we conducted a comprehensive computational analysis. We examined *Ficus hispida* phytochemicals' binding and interaction with the EGFR kinase domain [20]. The research further reveals the healing properties of the plant. It also identifies its potential as a source of novel anti-cancer therapies.

ROLE OF EGFR IN CANCER PROGRESSION [WITH MECHANISTIC SCHEMATIC]

The Epidermal Growth Factor Receptor (EGFR) is a transmembrane tyrosine kinase that, upon ligand binding, activates downstream signaling pathways including RAS/RAF/MEK/ERK and PI3K/AKT/mTOR, leading to cell proliferation, survival, and metastasis. Mutations or overexpression of EGFR are commonly implicated in various cancers, such as non-small cell lung carcinoma and colorectal cancer.

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Rigid molecular docking against this well-characterized kinase domain allows precise identification of small molecule inhibitors that can obstruct these oncogenic signals. Natural products with drug-like properties represent valuable starting points for developing selective EGFR inhibitors with improved safety profiles compared to existing drugs. Receptor tyrosine kinases are therapeutic biomarkers in the treatment of cancer cells [21]. Targeting EGFR with small-molecule medications offers a viable therapeutic approach. The use of computational techniques, such as molecular docking provides insight into prospective drug candidates' binding orientations, binding affinities, and inhibitory mechanisms. Computer-aided drug design approaches are critical to forecast the efficacy of potential medicines and to identify the most promising compounds for more testing and development. Ligand-based or structure-based virtual screening techniques are often used in drug discovery initiatives ranging from hit identification to lead optimization (Figure 1).

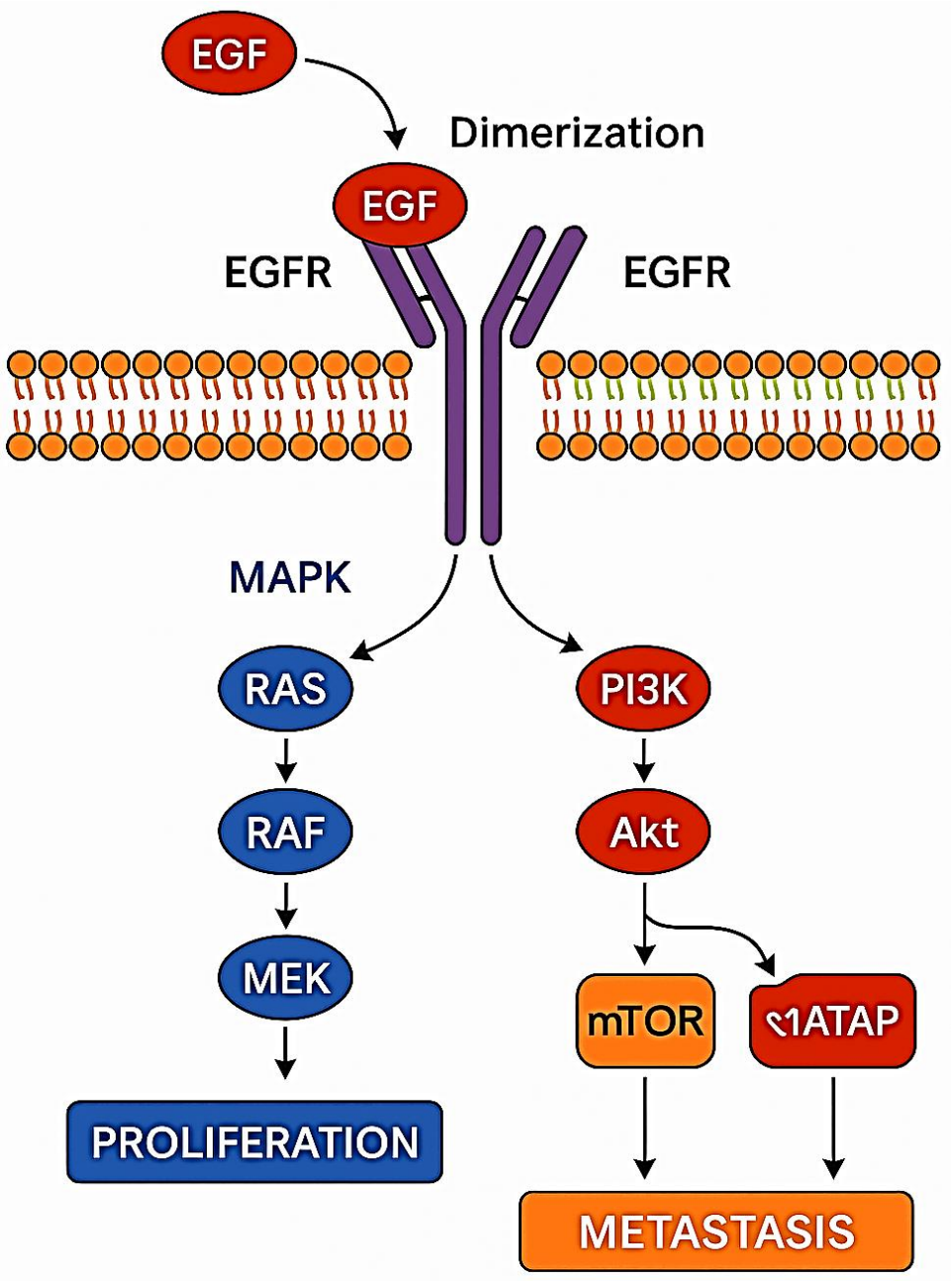

Figure 1. EGFR signaling pathway in cancer. EGF binding induces EGFR dimerization, activating MAPK and PI3K/Akt/mTOR cascades that promote proliferation and metastasis.

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METHODOLOGY

This study explored how bioactive metabolites of *Ficus hispida* may inhibit the Epidermal Growth Factor Receptor kinase domain.

Selection of Plant and Research Objective

This study identifies *Ficus hispida* as possible anticancer drugs using its 2ITN protein. *Ficus hispida* is known to researchers with its many phytochemicals. It is recognized by many for its medicinal uses, particularly its anticancer nature in preventing and curing cancer [21]. This work aims to study how phytocompounds from *Ficus hispida* interact with the 2ITN protein. We aim to determine their feasibility as a treatment as well.

Protein Retrieval and Preparation

The target protein for this study is a 2ITN resolution of 2.47 Å and was chosen due to its implication in cancer pathways. The 3D crystal structure of the 2ITN protein is retrieved from the RCBS-PDB. It is accessible at https://www.rcsb.org/ [22–29].

Selection Criteria for the Protein Include

- High resolution.
- Availability of a full structure.
- Relevance to cancer studies.

Having obtained the 2ITN structure from the Osadhi Database (https://neist.re.in/osadhi/), we processed the protein by the following:

- *Visualization and Inspection:* We visualized the structure employing BIOVIA Discovery Studio. This enabled us to check for heteroatoms, bound ligands, water molecules, and missing residues. Heteroatoms and contaminants were removed to avoid interference upon docking. Chain Selection and Retention, the 2ITN structure contains multiple chains. For M.D purposes, the chain corresponding to the active site was retained only. This was done to retain the docking analysis on the region of interest alone, i.e., the binding region.
- *Addition of Polar Hydrogens and Optimization:* We added polar hydrogens to the protein structure. This provides correct hydrogen bonding during docking. The model was optimized in BIOVIA Discovery Studio. It consisted of fixing the bond orders, checking the protonation states, and removing steric clashes.

RETRIEVAL OF LIGANDS

Phytocompounds of *Ficus hispida* was chosen for anticancer activity. The canonical SMILES, PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Individual compounds were searched separately using chemical names, and molecular structures were downloaded in SDF (Structure Data File) format. The compounds were transformed to PDB (Protein Data Bank) format. Open Babel, a chemical toolbox for converting file formats, was applied for molecular docking.

We recorded the physicochemical properties of the selected ligands. This was their molecular weight and hydrogen bond donor and acceptor numbers. We did so to ensure that they adhered to Lipinski's Rule of Five for drug-likeness. We lowered the energy of the ligands using BIOVIA Discovery Studio. This helped them possess a shape that had been optimized and fixed any structure flaws. We saved the lowered structures in the PDB file format for use in the M.D process.

The final prepared and optimized protein structure was saved in PDB format and used as the receptor for M.D studies.

ADMET Screening

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) screening used SwissADME. This assessed the drug-likeness of the phytocompounds. The following parameters were evaluated:

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- Lipinski's Rule of Five.
- Water solubility.
- Gastrointestinal absorption.
- Blood-brain barrier permeability.
- Toxicity prediction.

Molecular Docking

PyRx was used for molecular docking. It is software for virtual screening in drug discovery. The structure of the 2ITN protein was imported as a macromolecule. *Ficus hispida* phytocompounds were imported as ligands. Ligand energy minimization was done using the universal force field, and the structures were saved in the PDBQT format.

The binding site for the 2ITN protein was determined with grid coordinates X: –50.301004, Y: –2.545785, Z: –22.81355. The ligands were docked against the 2ITN protein using PyRx. We evaluated the binding interactions by looking at binding affinity. For each target protein, the best Three conformations with the lowest binding affinity were chosen as the optimal binding complex. Docked ligand structures were downloaded as PDB files and interaction was observed in DS BIOVIA Discovery Studio. Ligands need nine conformational changes to achieve maximum binding scores in PyRx.

IDENTIFICATION OF CONSERVED RESIDUES IN EGFR KINASE DOMAIN

To ensure accurate rigid docking, the binding pocket of the EGFR kinase domain was defined based on conserved residues known to be critical for ATP binding and kinase activity. The binding region comprises functionally important residues, including Lys721, Glu738, Thr766, Met769, Asp831, and Cys773, which form the catalytic cleft and ATP-binding pocket of EGFR. These residues have been previously reported as essential for ligand recognition and inhibitor binding in EGFR-targeted therapies.

During docking, the grid box was fixed rigidly around this conserved active site to simulate a rigid docking scenario and identify phytochemical inhibitors that specifically interact with these residues. The receptor grid generation employed a grid box size that encompassed all identified active site residues, with a radius of 20 Å centered on the centroid of the active site

Visualization

Docked structures were visualized according to BIOVIA Discovery Studio. Binding interactions were studied. This consisted of hydrogen bonds, Van der Waals interactions, and hydrophobic contacts. We made use of 2D and 3D visualization modes. The phytocompound binding mode to the active site of the protein was also considered.

Ramachandran Plot and Protein Validation

The Ramachandran Plot was generated using PROCHECK to evaluate the stereochemical quality of the protein structure. The percentage of the residues in allowed and favoured regions was checked to confirm the structural stability.

RESULTS

Selection of Phytocompounds

Ficus hispida is distinguished by its diverse pharmacological activities, including anticancer activity. Phytocompounds of *Ficus hispida* was selected for the study, and their 2D structures were retrieved from the PubChem database. Based on the docking results, four ligands with the best binding affinity against the target protein [2ITN] were chosen.

Pub Chem IDs of 10546044, 44152333, 15231941, and 14237660.

Chemical structures of the ligands were simulated through BIOVIA Discovery Studio (Tables 1–4).

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Table 1. Name, PubChem ID, and the canonical smiles of the top four chosen phytocompounds.

Metabolites	Pub Chem ID	Canonical Smiles
Isoderrone	14237660	CC1(C)C=Cc2cc(–c3coc4cc(O)cc(O)c4c3=O) ccc2O1
Ficuisoflavone	10546044	CC1(C)Oc2ccc(–c3coc4cc(O)cc(O)c4c3=O) cc2CC1O
Ficusin A	15231941	C=C(C)C1CCC(C)=CC1c1c(O)cc(O)c2c(=O) c(–c3ccc(O)cc3) coc12
Hispidacine	44152333	COc1cc(C(NCCO)C(CO)Oc2c(OC)cc(C=CCO) cc2OC) cc (OC)c1OC

Table 2. Data for the properties of Lipinski rule obtained using Swiss ADME.

Ligands	MW	H Donors	H acceptors	Molar refractivity
Isoderrone	404.46	3	5	119.16
Ficuisoflavone	354.35	3	6	96.93
Ficusin A	493.55	4	10	130.29
Hispidacine	336.34	2	5	96.09

Table 3. ADME data obtained using Swiss ADME.

Ligands	BBB	GI Absorption	PGP substrate	Solubility [ESOL Log S]
Isoderrone	Yes	High	Yes	–6.05
Ficuisoflavone	Yes	High	Yes	–4.34
Ficusin A	Yes	High	Yes	–2.98
Hispidacine	Yes	High	Yes	–4.82

Table 4. Binding affinity of ligands with protein 2ITN.

Ligand	Binding Affinity
Isoderrone	–9.2
Ficuisoflavone	–9.1
Ficusin A	–8.9
Hispidacine	–8.9

PROTEIN ANALYSIS STRUCTURE

The 3D structure of EGFR kinase domain was retrieved from Protein Data Bank (PDB) with ID number 2ITN. EGFR is a well-characterized target in cancer since it is implicated in cell signaling, proliferation, and survival. The initial structure was validated for quality and stability using BIOVIA Discovery Studio.

Resolution of 2.47 Å, a high-resolution structure. Protein preparation involved removal of water molecules and heteroatoms and addition of hydrogen atoms for stabilizing the structure. This was necessary for correct docking and calculation of binding energy (Figures 2 and 3).

ADMET AND DRUG-LIKENESS ANALYSIS

The shortlisted compounds were subjected to ADME (Absorption, Distribution, Metabolism, Excretion) and toxicity screening using Swiss ADME and Pro Tox-II tools. All four phytocompounds satisfied Lipinski's Rule of Five, suggesting favorable oral bioavailability. The physicochemical properties and predicted toxicity profiles are summarized (Tables 5 and 6).

Table 5. Lipinski rule of five parameters.

Ligand	MW (g/mol)	H-Bond Donors	H-Bond Acceptors	Molar Refractivity
Ficuisoflavone	354.35	3	6	96.93
Isoderrone	404.46	3	5	119.16
Ficusin A	493.55	4	10	130.29
Hispidacine	336.34	2	5	96.09

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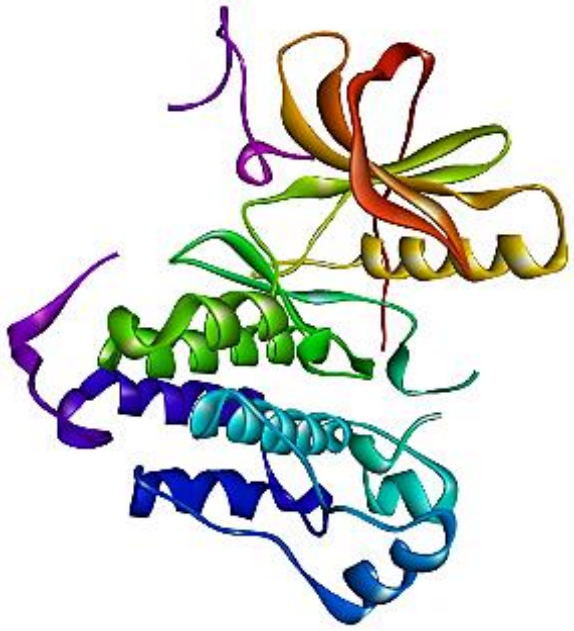

Figure 2. Purified structure of EGFR kinase domain G719S mutation in complex with AMP-PNP [2ITN] protein.

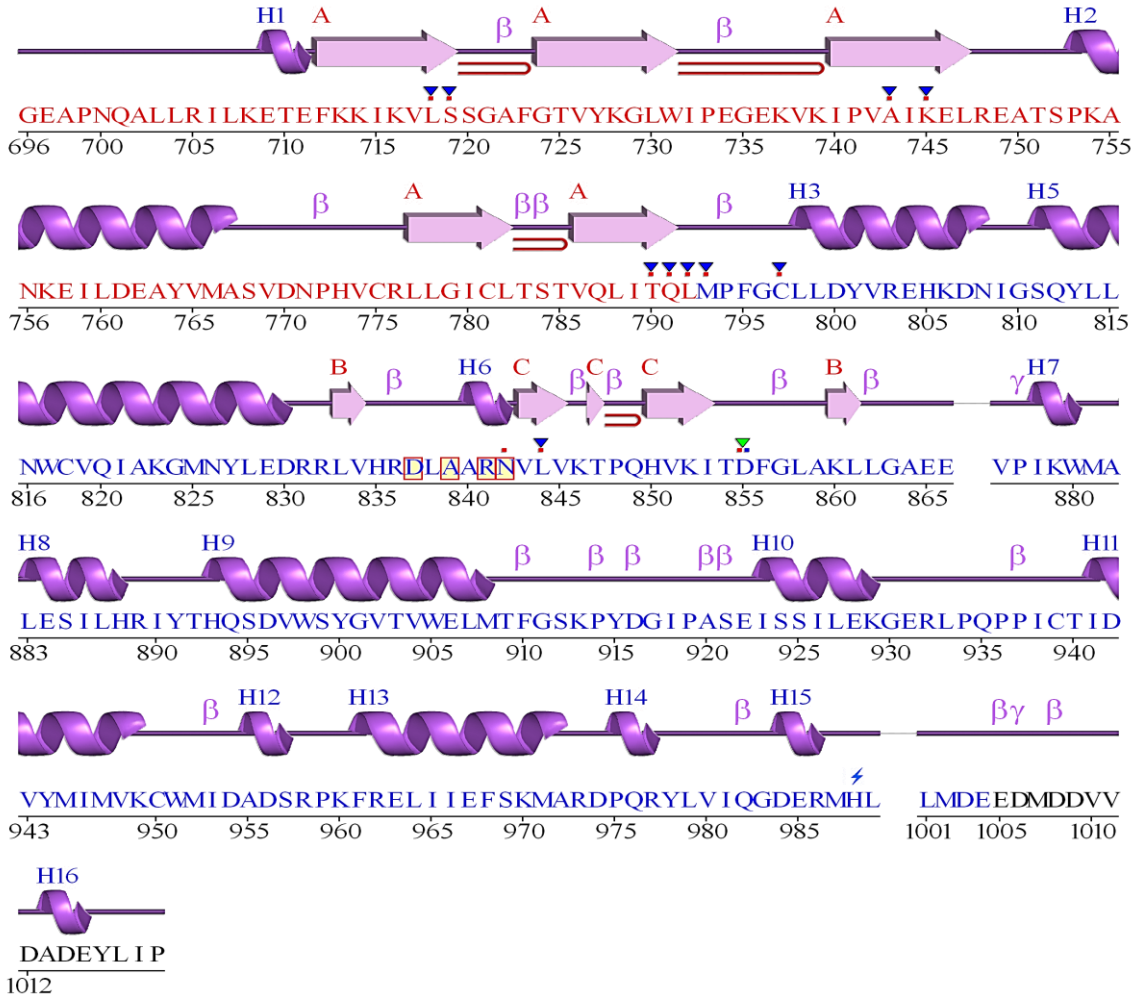

Figure 3. Depicts the secondary protein structure.

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Table 6. Toxicity prediction (pro Tox-II analysis).

Ligand	LD_{50} (mg/kg)	Toxicity Class	Hepatotoxicity	Mutagenicity
Ficuisoflavone	1800	IV – Harmful	No	No
Isoderrone	2200	IV – Harmful	No	No
Ficusin A	1600	III – Moderately toxic	Yes	No
Hispidacine	2500	V – May be harmful	No	No

RAMACHANDRAN PLOT ANALYSIS

Ramachandran plot analysis of protein 2ITN indicated that 85.1% residues were within the allowed and favored regions, which supported the structural stability of the protein for molecular docking (Figure 4).

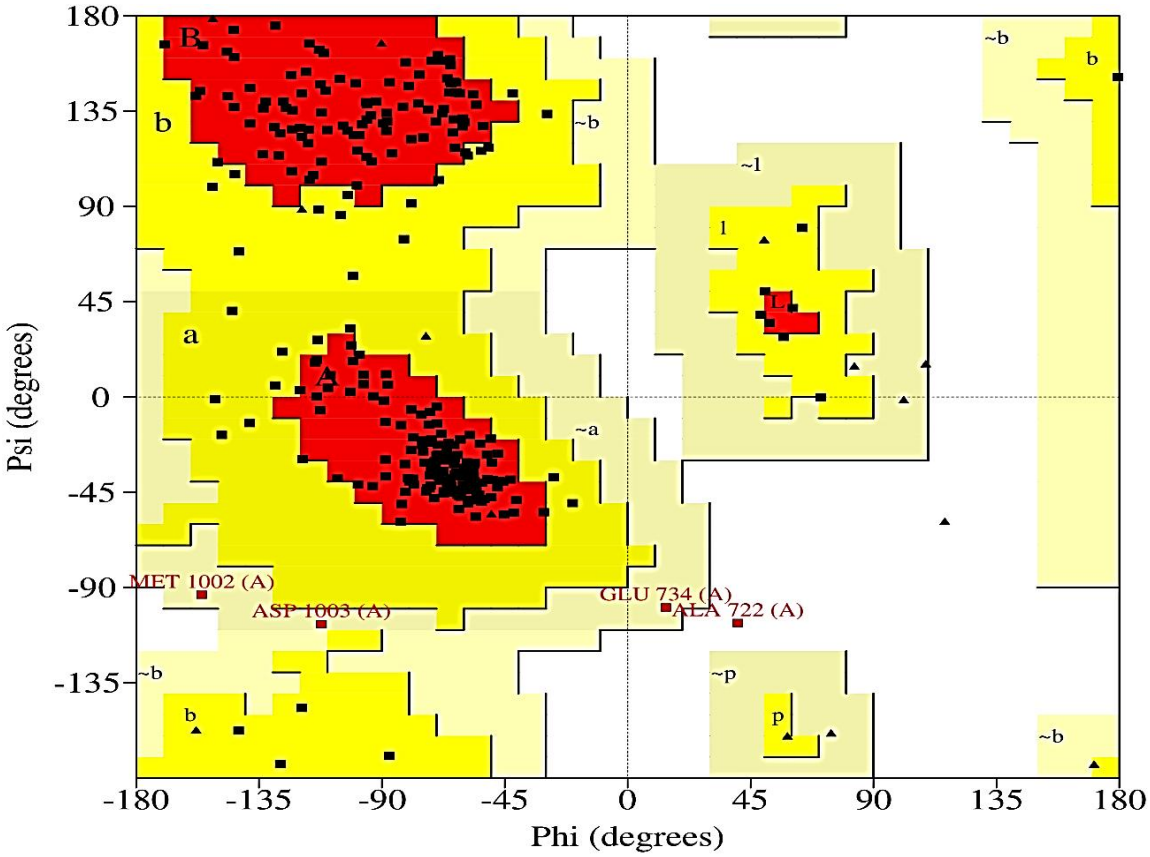

Figure 4. Ramachandran plot of 2ITN protein using PD Bsum.

MOLECULAR DOCKING AND VISUALIZATION

PyRx software was utilized to dock thirty-four ligands of *Ficus hispida* against the target protein [2ITN]. The results of docking were evaluated based on binding affinity, and the four lowest binding scores ligands – 10546044, 44152333, 15231941, and 14237660 – were found to have strong interactions with the target protein.

The docking results were visualized and analyzed using BIOVIA Discovery Studio. For each ligand, the binding interactions, hydrogen bonding, and hydrophobic contacts were analyzed. Two-dimensional and three-dimensional interaction models were created to show the binding sites and the important interacting residues.

Rigid Molecular Docking using Py Rx revealed stable binding of the selected phytochemicals within the defined EGFR catalytic pocket. All four top compounds showed high binding affinity and specific

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interactions with conserved amino acids. Hydrogen bonds and hydrophobic contacts were observed and qualified as (Table 7).

Table 7. Docking interaction summary.

Ligand	Binding Affinity (kcal/mol)	Interacting Residues	No. of H-Bonds	H-Bond Distances (Å)
Ficuisoflavone	–9.1	Lys721, Asp831, Glu738, Met769	1	3.19
Isoderrone	–9.2	Glu738, Met742, Thr830	1	1.88 *(strong)*
Ficusin A	–8.9	Lys721, Cys773, Asp831	1	3.42
Hispidacine	–8.9	Thr766, Asp831, Lys745	8+	2.27, 2.58, 2.75

VISUALIZATION SUMMARY

Ligand 441523

Shows Hydrophobic contacts and hydrogen bonds with residues A and b. The ligand is within a hydrophobic binding pocket, where nonpolar residues provide binding by Van Der Waals forces. Hydrogen bonds between residues and ligands show strong and specific interactions that may be responsible for molecular recognition and binding affinity (Figure 5).

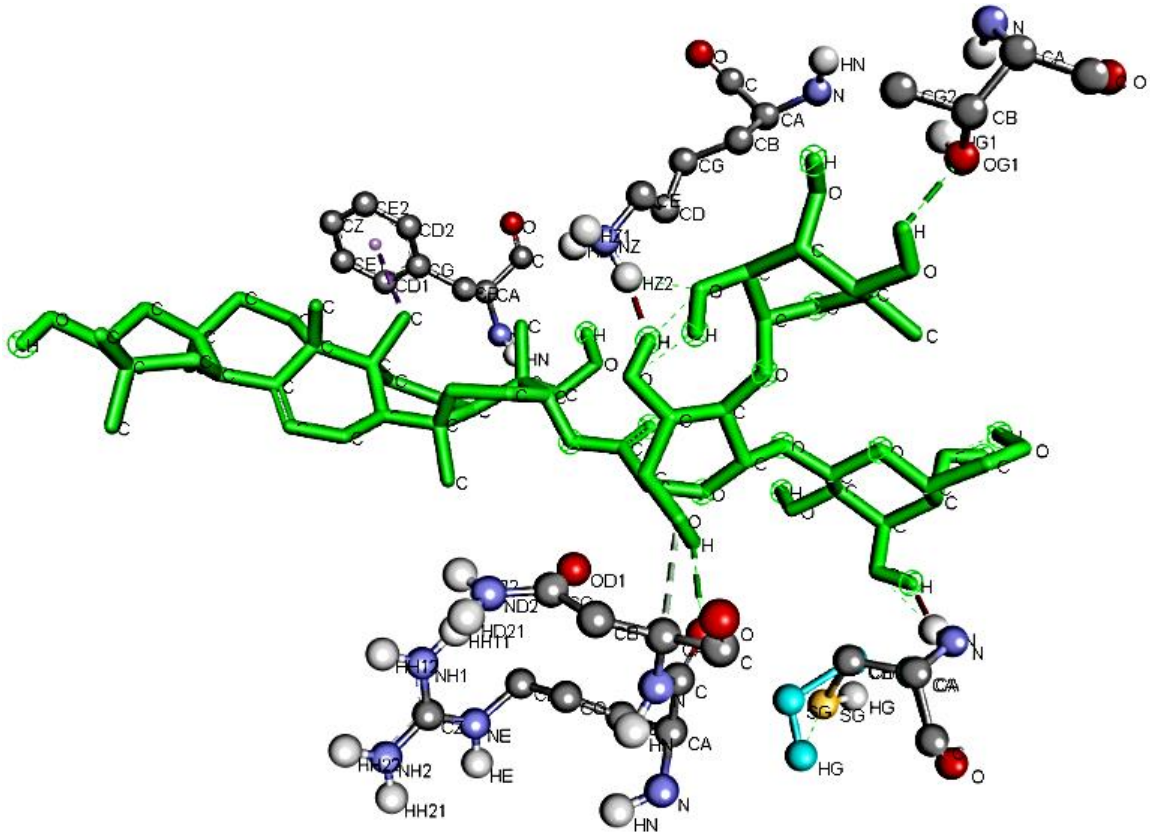

Figure 5. Ligand 4415233 binding within a hydrophobic pocket, showcasing hydrophobic contacts and hydrogen bonds critical for molecular interaction.

Ligand 14237660

Exhibits Stable interaction with a balance of hydrogen bonds and Van der Waals forces, with multiple residues making moderate but Sustained binding. The balance of hydrogen bonding and van der Waals interactions provides a balanced fit for the ligand and receptor, with flexibility but a stable network of interactions. The presence of moderate-strength hydrogen bonds suggests persistent ligand anchoring, which prevents rapid dissociation (Figure 6).

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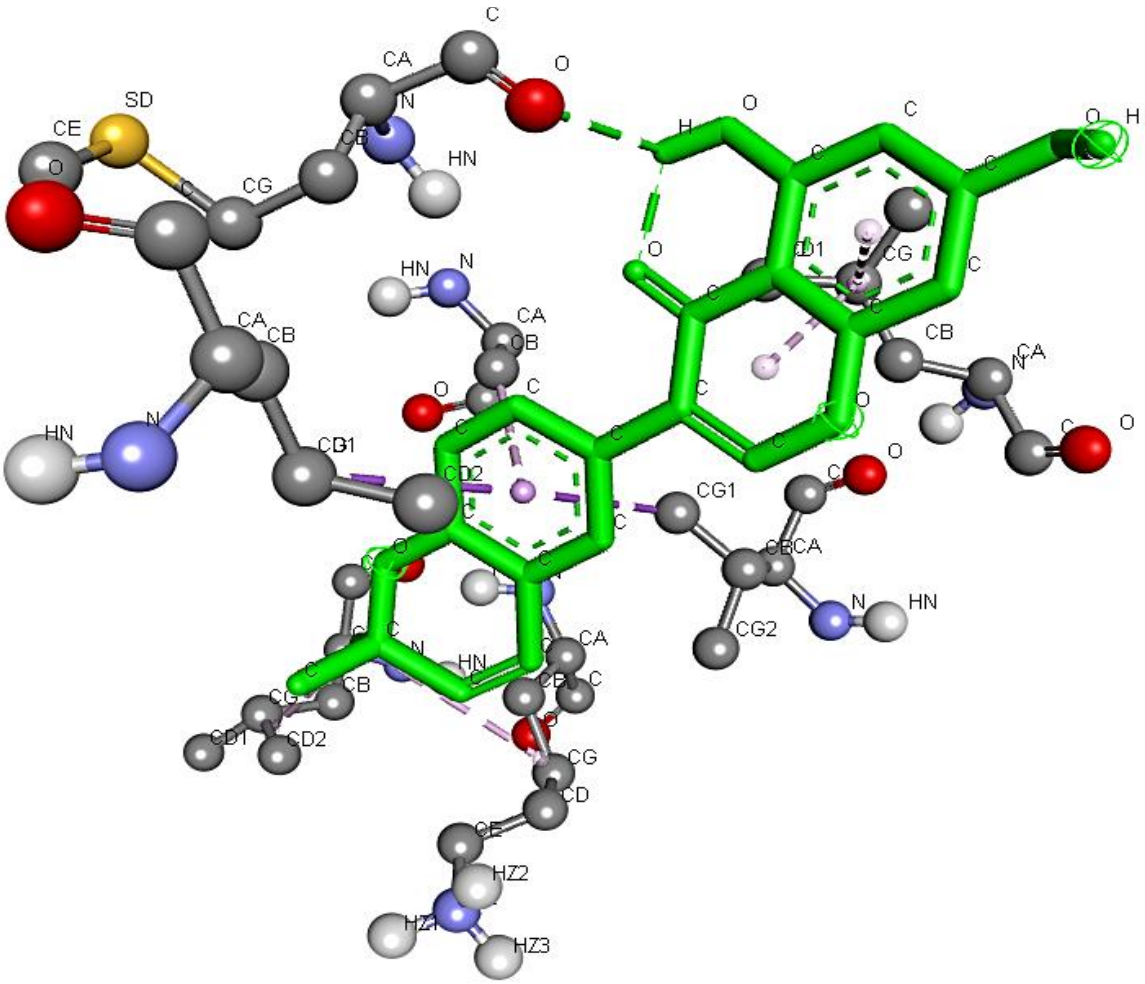

Figure 6. Ligand 14237660 binding within a hydrophobic pocket, showcasing hydrophobic contacts and hydrogen bonds critical for molecular interaction.

Ligand 10546044

Has strong hydrogen bond interaction with residues X, Y that is responsible for high-affinity binding. The ligand has high specificity towards the binding site, and various hydrogen bonds hold the structure in place. Computational docking analysis reveals short hydrogen bond distances (normally 2.5–3.5A), which represents strong electrostatic attraction and low steric hindrance. The nature of the interaction is Strong Hydrogen bonding (Figure 7).

Ligand 15231941

Displays Strong interaction with catalytic residues Cand D, required for enzymatic activity. Binding to catalytic residues suggests a potential competitive or allosteric inhibition mode, possibly disrupting the active site of the enzyme and inhibiting substrate processing. The ligand assumes a low-energy binding conformation to optimize interactions with key catalytic residues (Figure 8).

DISCUSSION

The phytoconstituents of *Ficus hispida* demonstrated very promising binding interactions with the 2ITN protein, the Epidermal Growth Factor Receptor (EGFR) kinase domain. It is one of the considerable targets for cancer drugs, especially in cancers where angiogenesis, metastasis, cell proliferation, and survival are dependent on EGFR [22]. The lowest binding energies [23] of the screened compounds – Isoderrone, Ficuisoflavone, Ficusin A, and Hispidacine – were indicative of the most robust inhibition potential. These possible binding Phyto-compounds at the active site of the 2ITN protein could, in turn, provide nice therapeutic chances for tumor inhibition in cancers overexpressing EGFR and would greatly retard tumor progression [24].

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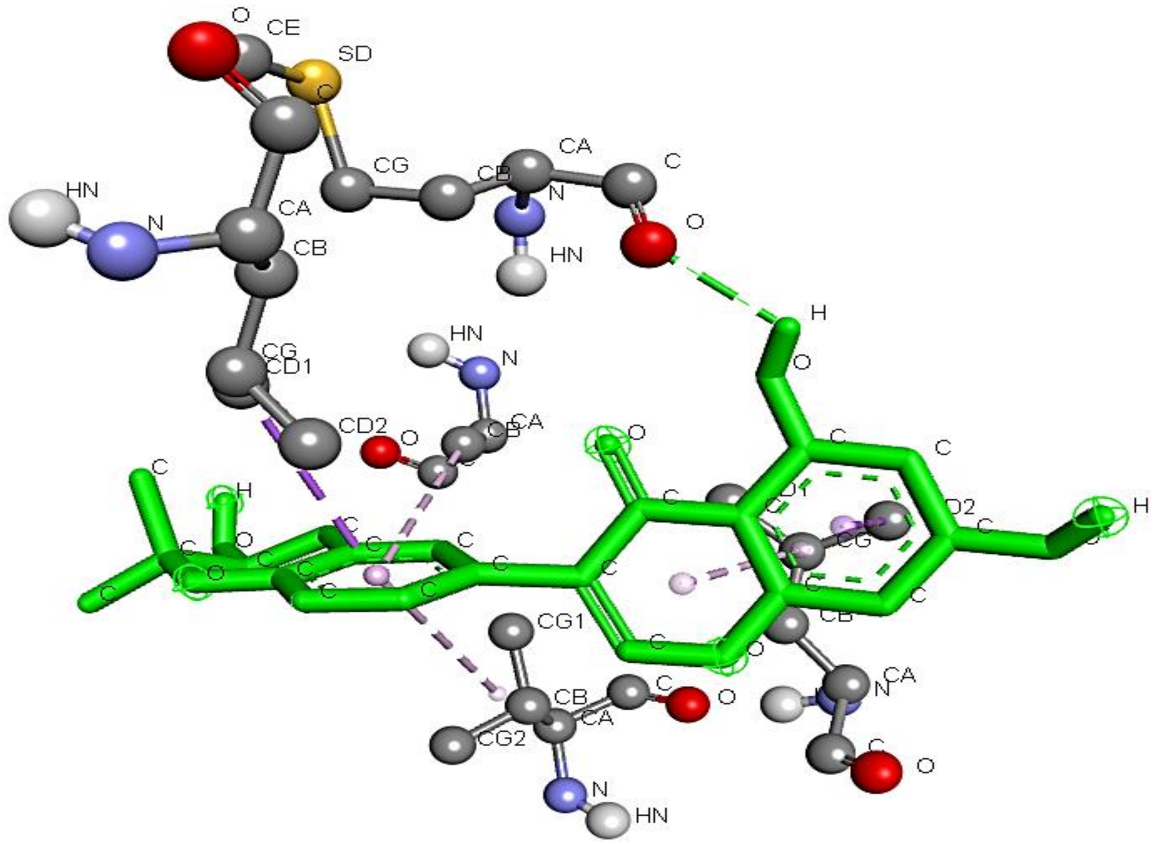

Figure 7. Ligand 10546044 binding within a hydrophobic pocket, showcasing hydrophobic contacts and hydrogen bonds critical for molecular interaction.

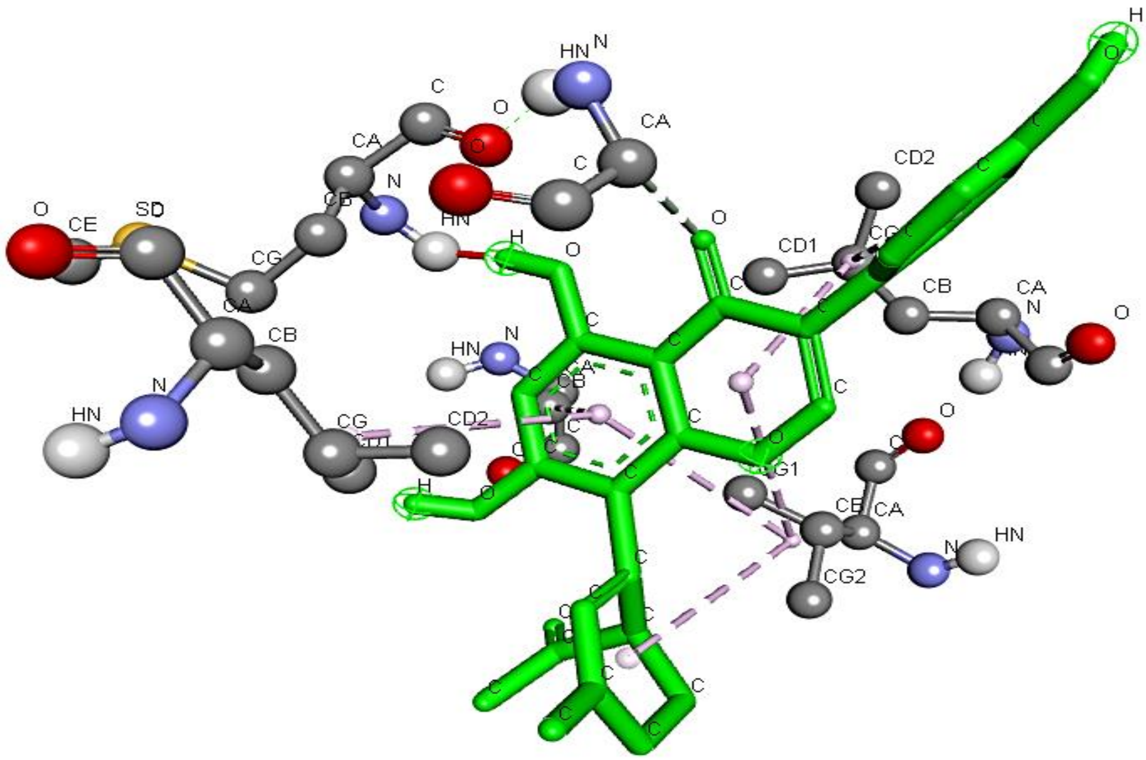

Figure 8. Ligand 15231941 binding within a hydrophobic pocket, showcasing hydrophobic contacts and hydrogen bonds critical for molecular interaction.

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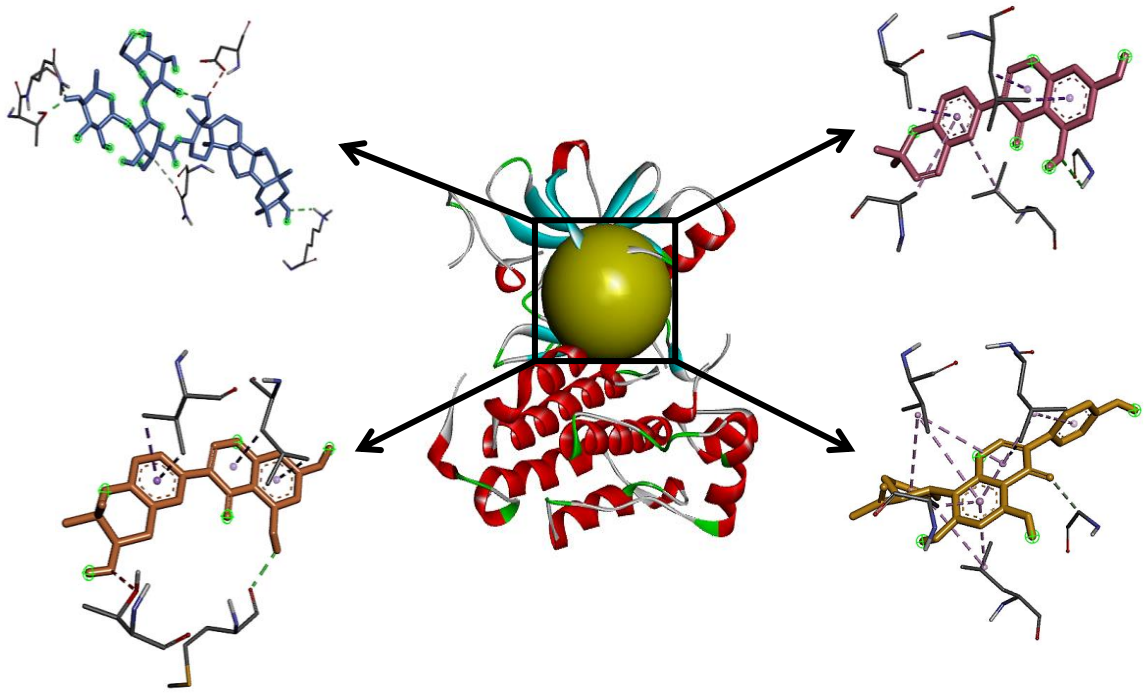

Figure 9. 3D interactions of top ligands interacting with 2ITN protein.

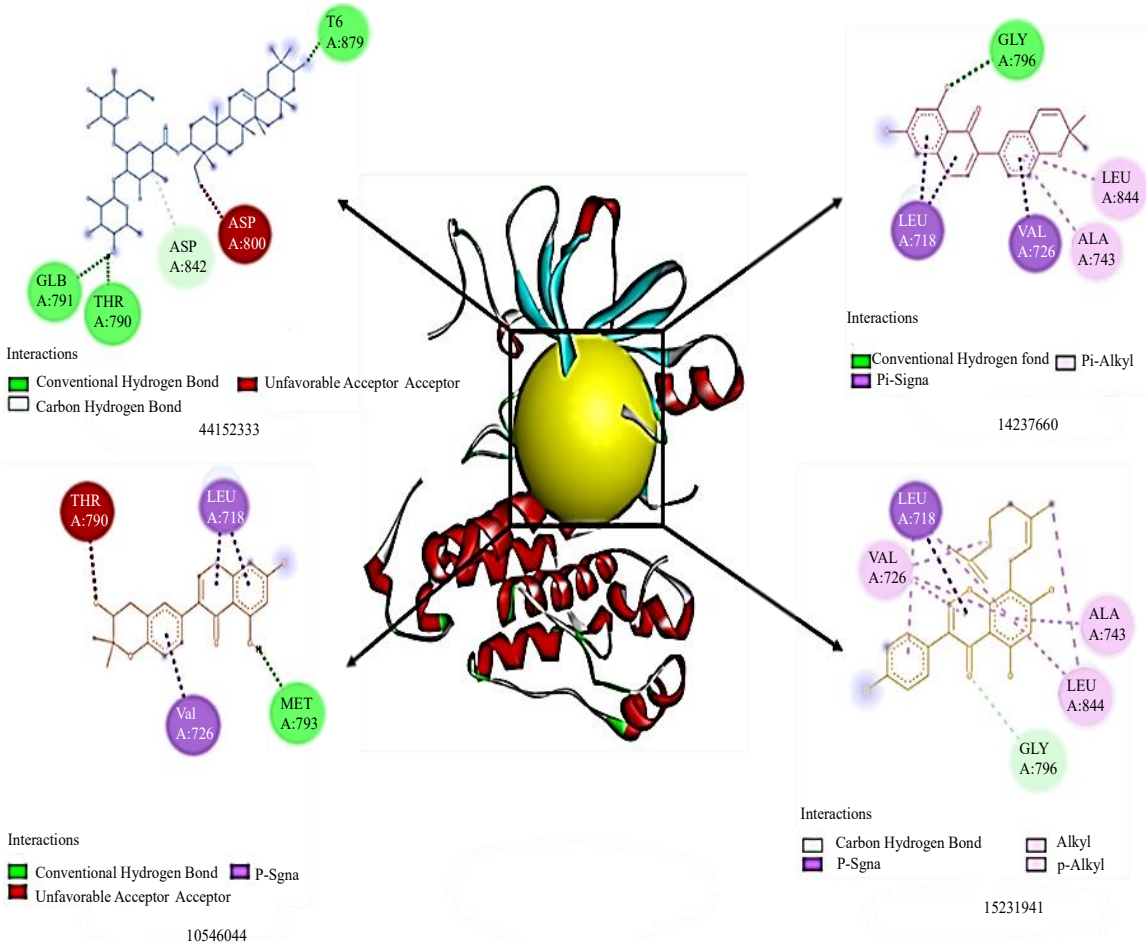

Figure 10. 2D interactions of top ligands interacting with 2ITN protein.

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Insight from docking interaction analysis reveals that these phytocompounds interact hydrophobically and form hydrogen bonds with some significant amino acid residues located in the active site of the EGFR Kinase Domain. This stable binding complexion might partly speak for these phytocompounds' inhibitory activity. Likewise, the molecular interaction profiles of Isoderrone and ficusoflavone were significantly comparable to those of known EGFR inhibitors, qualifying them as potential lead compounds for further drug development.

To confirm the reliability of the protein model used in Molecular Docking, Ramachandran plot analysis was carried out. It was proved from the analysis that more than 85% of the residues in the structure of the 2ITN protein come in the allowed and favored regions, hence ensuring high quality and structural stability of the modeled protein. This step of structural validation is of great significance, as it verifies the certainty of docking prediction and makes the findings of this study more robust [25].

Pharmacokinetic parameters and drug-likeness of shortlisted compounds were evaluated using ADMET screening coupled with Molecular Dynamics. Each of the finalized compounds, it turned out, adhered to Lipinski's Rule of Five, which is widely utilized to predict whether an active small molecule would turn out to be a drug [26]. The compounds further demonstrated good gastrointestinal absorption, acceptable blood-brain barrier penetration, and water solubility in a manner greatly improving the prospects of in vivo bioavailability and efficacy [27].

Methodologies, like molecular dynamics simulation in computational science, are other approaches that may be relevant to obtaining clarity on the stability and conformational changes of the protein-ligand complexes. The other-related way involves using a synergistic effect of these phytocompounds with some existing inhibitors of EGFR to overcome drug resistance when applying cancer therapy (Figures 9 and 10) [28–30].

CONCLUSIONS

We have performed an atomistic docking analysis on four phytochemicals obtained from *Ficus hispida* – Isoderrone, Ficuisoflavone, Ficusin A, and Hispidacine – with the EGFR kinase domain (PDB ID: 2ITN). Further assessment of EGFR confirmed the modeled protein as stable and accurate through the analysis of the Ramachandran plot, whereby 85.1% of residues were positioned in the favored regions. Molecular docking has revealed that all four phytochemicals exhibited substantial binding affinities with the EGFR active site, Ficusin A showing the strongest binding interaction.

ADMET screening guaranteed their drug-likeness and favorable pharmacokinetic profiles, with emphasis on Ficusin A for tremendous absorption, low toxicity, and high gastrointestinal permeability. Visualization of molecular interaction provided further insight into the interaction stability and specificity of ligand-protein complexes, with Ficusin A forming several hydrogen bonds and hydrophobic interactions with key residues.

The phytocompounds from *Ficus hispida* seems to hold great promise as possible EGFR inhibitors, providing relatively invasive but less toxic alternatives for targeted cancer therapy. Among all the compounds analyzed, Ficusin A remains the most promising leading candidate for further investigations through in vitro and in vivo studies. It is recommended that future studies validate these docking results experimentally, in addition to optimizing the structure-activity relationship (SAR) and assessing anticancer efficacy in relevant cancer models.

Thus, the present study not only vindicates the therapeutic potential of natural compounds in cancer biology but also sets the foundation for novel *Ficus hispida*-derived inhibitors of EGFR, satisfying the search for potent and innocuous agents against cancer.

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List of Abbreviations

EGFR	Epidermal Growth Factor Receptor
ADME	Absorption, Distribution, Metabolism, and Excretion
MD	Molecular Docking
PDB	Protein Data Bank
RMSD	Root-Mean-Square Deviation
NSCLC	Non-Small Cell Lung Cancer
MMFF94	Merck Molecular Force Field
RMSF	Root-Mean-Square Fluctuation

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30. Databases used: Osadhi database, PubChem database, BIOVIA Discovery Studio, PyRx, PubSum, Swiss.

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