

In Silico Investigation of *Aristolochia longa* Anticancer Potential against the Epidermal Growth Factor Receptor (EGFR) in the Tyrosine Kinase Domain

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Abstract: This study employed *in silico* methods to identify potential therapeutic targets for the inactive EGFR tyrosine kinase domain in complex with Erlotinib (PDB: 4HJO) which is known to cause cancer, using natural extracts from *Aristolochia longa* root. A library comprising five natural compounds (Luteolin, 4-hydroxycinnamic acid, Kaempferol, ferulic acid, citric acid, and quinic acid) and the standard Erlotinib (control) were subjected to Lipinski's rule of five, ADMET parameter analyses, molecular docking and molecular dynamics simulation. Results revealed comparable pharmacological responses between the five compounds and the standard drug, demonstrating promising outcomes without limitations. Notably, Luteolin, Kaempferol, and quinic acid exhibited higher binding energies than the reference molecule, with binding affinities of -9.083 kcal/mol, -8.260 kcal/mol, and -5.857 kcal/mol, respectively. Molecular dynamics simulations confirmed the stability of the most effective EGFR protein-ligand, displaying consistent interaction profiles, favorable molecular properties, and a stable trajectory (RMSD, RMSF). Overall, these *in silico* analyses highlight the potential of aromatic and medicinal plant-derived compounds to inhibit EGFR protein associated with cancer development, emphasizing the need for further *in vitro* and *in vivo* investigations to explore their therapeutic applications in cancer patients.

Keywords: *Aristolochia longa*, EGFR receptor, Anticancer, ADMET analysis, Molecular docking and Molecular dynamics simulation.

1. Introduction

The *Aristolochiaceae* family, comprising a diverse range of plant species, has attracted significant attention due to its potential therapeutic properties (Patel *et al.*, 2022). With approximately 500 species distributed across various geographical regions, including tropical, subtropical, and Mediterranean countries, this family demonstrates a broad distribution (Wiert, 2007). Members of the

Aristolochiaceae family have been documented in forests spanning America, Asia, Africa, Europe, and sporadically on other continents, indicating their adaptability and global presence (Blondel & Aronson, 1999). *Aristolochia longa*, a notable species within the Aristolochiaceae family, predominantly inhabits the Mediterranean region, particularly North Africa (Bouhaous *et al.*, 2022). Locally referred to as "Barraztam" in folklore (Ghadi *et al.*, 1999), this species has been utilized since ancient times for its purported medicinal benefits in treating ovarian insufficiency and snake bites (Tovar & Petzel, 2009). The enduring recognition of *Aristolochia longa* as a valuable medicinal resource deeply rooted in traditional knowledge emphasizes its historical significance (Hoffmann *et al.*, 2003). In recent years, scientific investigations have aimed to unravel the bioactive compounds present in *Aristolochia longa* and explore their pharmacological activities (Zhou *et al.*, 2017). Of particular interest are the root extracts of this plant, which have exhibited remarkable antioxidant, antibacterial, and anticancer properties (Ozen *et al.*, 2020). Antioxidants are crucial in neutralizing harmful free radicals, mitigating oxidative stress and preventing cellular damage (Sen & Chakraborty, 2011). The presence of potent antioxidants in *Aristolochia longa* root extracts suggests their potential as therapeutic agents in combating oxidative stress-related disorders (Mishra *et al.*, 2021).

Furthermore, *Aristolochia longa* root extracts have demonstrated promising antibacterial activity against various pathogenic microorganisms (Ozen *et al.*, 2020). With the escalating prevalence of antibiotic resistance, the search for alternative antimicrobial agents has become imperative (Mickimaray *et al.*, 2020). The antimicrobial potential exhibited by *Aristolochia longa* suggests its possible utility as a natural source for novel antibacterial compounds (Dossey, 2013). Another intriguing aspect of *Aristolochia longa* is its potential anticancer activity (Madani *et al.*, 2022). Cancer remains a significant global health burden, necessitating the continuous exploration of novel anticancer agents (Lui & Dong, 2021). Investigations of *Aristolochia longa* root extracts have revealed their ability to inhibit cancer cell growth and induce apoptosis, promising future use in cancer treatment strategies (Marzuki *et al.*, 2023). Summarily, the Aristolochiaceae family encompasses numerous plant species distributed across diverse regions worldwide (Ehrlich & Raven, 2011). Recent scientific studies have highlighted the exceptional antioxidant, antibacterial, and anticancer activities associated with *Aristolochia longa* root extracts (Dai *et al.*, 2022).

Further research and exploration of this plant species hold the potential to unlock its therapeutic benefits, leading to the development of novel treatments for various health conditions (Taibi *et al.*, 2021). *Aristolochia longa* has garnered significant scientific attention and is extensively studied in the literature as a plant species. The wealth of research on this plant, particularly its phytochemical composition, is evident from bibliographic evidence (Vahekeni *et al.*, 2020). Phytochemical analysis of *Aristolochia longa* has identified several major bioactive compounds, including luteolin, 4-hydroxycinnamic acid, kaempferol, ferulic acid, citric acid, and quinic acid (Omari *et al.*, 2020). These compounds have attracted interest due to their potential pharmacological activities. Investigations have revealed that *Aristolochia longa* exhibits significant efficacy against EGFR (Epidermal Growth Factor Receptor) tyrosine kinase mutations or overexpression (Dhanasekaran *et al.*, 2016). Such genetic alterations and protein dysregulation are associated with the development and progression of various types of cancer.

Recent research on the anticancer properties of *Aristolochia longa* included an in-depth study of its phytochemical composition and potential therapeutic uses. The study focused on methanolic and aqueous root extracts, determining polyphenols and flavonoids, and evaluating antioxidant, antitumor, and antibacterial activities. This study advanced current knowledge by identifying key compounds, high polyphenol concentrations, and potent inhibitory effects, highlighting *A. longa*'s potential as a

natural remedy in cancer prevention and treatment, enhancing understanding of its anticancer properties.

Understanding the therapeutic potential of *Aristolochia longa* in targeting these molecular abnormalities related to cancer is paramount for advancing our knowledge and exploring potential treatment strategies (Ultich *et al.*, 2019). The present research article investigates the potential pharmacological activities of a library of major bioactive compounds, namely luteolin, 4-hydroxycinnamic acid, kaempferol, ferulic acid, citric acid, and quinic acid. In addition, the study employs erlotinib, an established inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase pathway, as an anticancer control for comparative analysis (Huang *et al.*, 2004) to evaluate the interactions and binding affinities of these compounds an *in-silico* approach was employed, encompassing key steps such as the assessment of ADMET parameters and adherence to Lipinski's rule of five, molecular docking analysis, and molecular dynamics simulation for a duration of 100 nanoseconds (Rao & Srinivas, 2011). By employing these computational techniques, a comprehensive understanding of these compounds' potential efficacy and mechanisms of action can be obtained, offering valuable insights for further exploration and development of novel therapeutic agents (Li, 2016).

2. Materials and methods

2.1. Ligands preparations and ADMET properties assessment

To enhance and minimize the energy of compounds such as luteolin, 4-hydroxycinnamic acid, kaempferol, ferulic acid, citric acid, and quinic acid **Fig. 1.**, we utilized the LigPrep module with the Maestro program (Omer *et al.*, 2022), erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase pathway is used as an anticancer control (Huang *et al.*, 2004). The energy minimization and optimization process was carried out using the OPLS_2005 force field (Bourhou *et al.*, 2023), and hydrogen atoms were incorporated while eliminating salt and ionization at pH (7 ± 2). The QikProp (Dash *et al.*, 2015) module of Schrödinger was used to investigate the absorption, digestion, metabolism, excretion, and toxicity (ADMET) properties of all compounds. The output files can be saved using the PDB format, which is compatible with any visualization application for validation. The research discovered significant physicochemical characteristics, such as elasticity, molecular weight/size, hydrophobicity, bioavailability, permeability, and polar solubility. The compounds were scrutinized with the utmost care, and those with the highest level of scrutiny were evaluated for potential violations of Lipinski's rule of five.

2.2. Molecular docking and preparation of protein

Docking is a method used to calculate the preferred orientation of a molecule when bound to a second molecule to form a stable complex. In this study, the Crystal structure of the inactive EGFR tyrosine kinase domain with Erlotinib (PDB: 4HJO) was selected for analysis (**Fig. 2**) with a resolution of 2.75 Å, R-Value Free of 0.253, R-Value Work of 0.230, and Observed R-Value of 0.231, mutations or overexpression of this protein have been implicated in various types of cancer. The protein structure was obtained from the Protein Data Bank (PDB) (Park *et al.*, 2012), and the active site was selected as the target center. The dimensions of the central grid were chosen to encompass all atoms of the ligand, which was defined using the coordinates ($x=23.48$, $y=9.72$, and $z=59.32$). The Protein Preparation Wizard (Maestro12.8, Schrodinger2021-2) (Diass *et al.*, 2023) was used to prepare the protein structure.

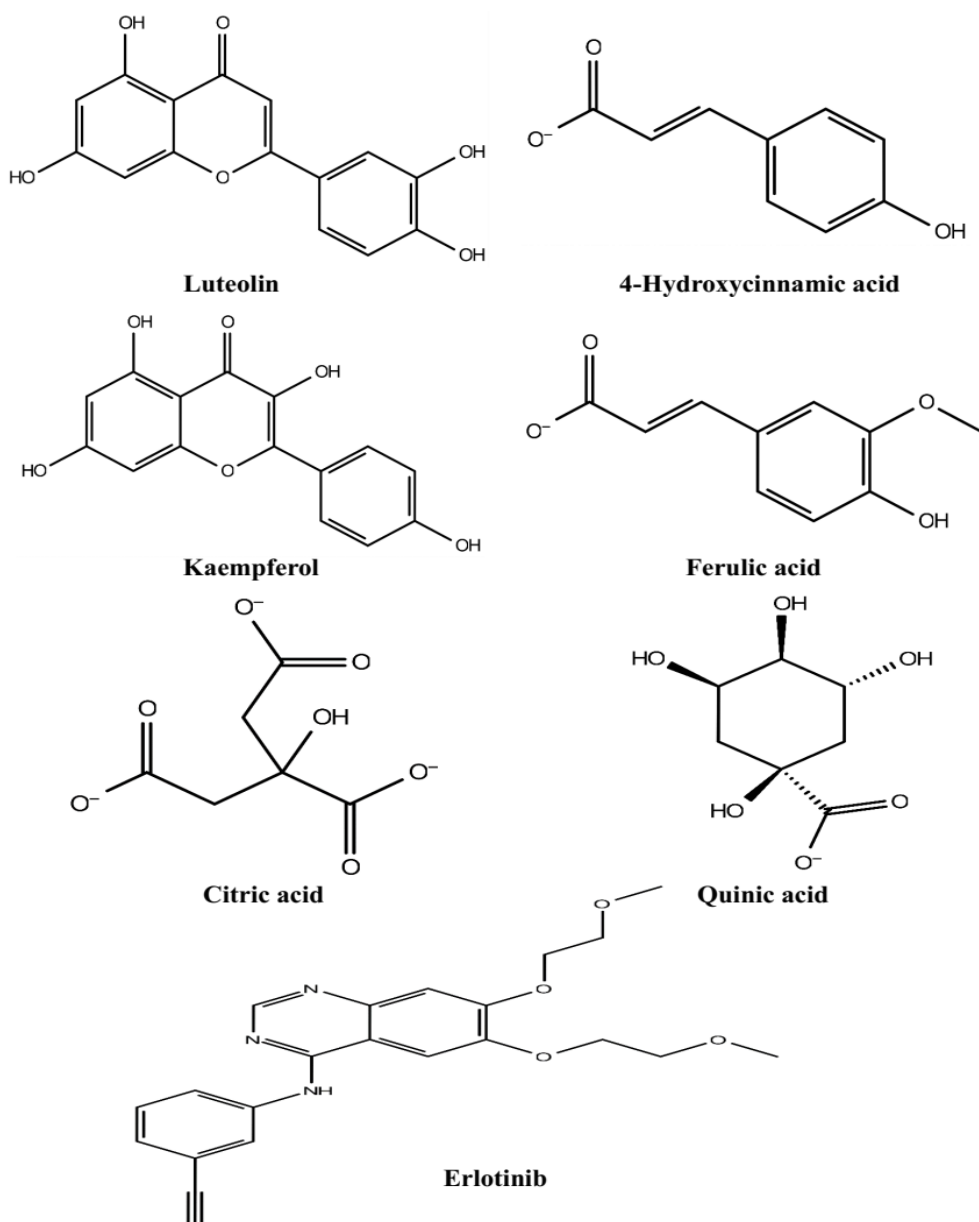


Fig. 1. Structure of main drug molecules

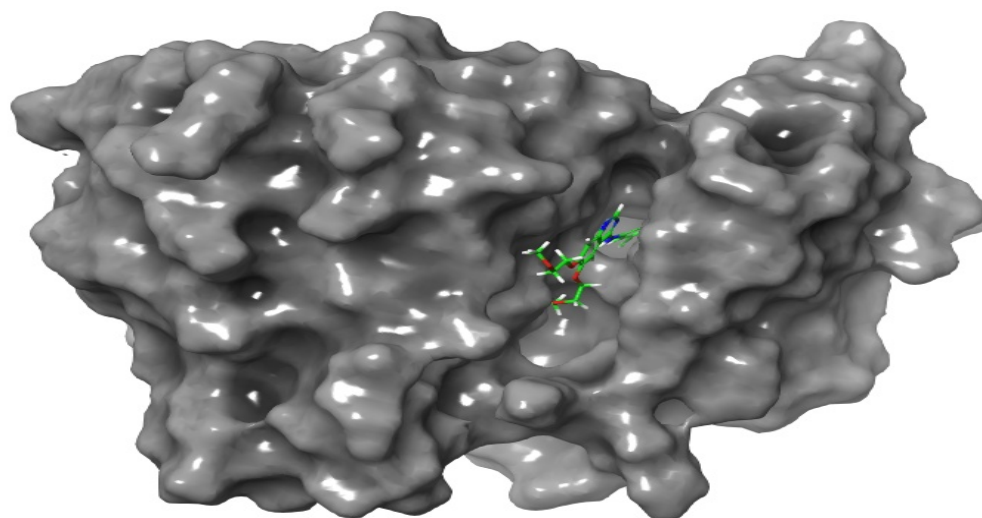


Fig. 2. The Crystal structure (Solid Surface) of the inactive EGFR tyrosine kinase domain with Erlotinib (PDB: 4HJO)

The ligand and water atoms were removed, and non-polar hydrogens were merged. Personalized hydrogen atoms were also added to the protein binding orders, and we generated hot states using Epik with pH set to (7 ± 2) . The energy minimization was performed using the OPLS_2005 force field, and the protein structure was minimized by default, limiting RMSD to 0.3 Å. Finally, the XP (extra precision) glide score was utilized to predict the binding affinity of the selected anchored poses. The output docking scores were defined as affinity binding (Kcal/mol), and the best final conformation with the minimum binding energy was selected. The interaction of the ligand with the active site residues was then visualized using both two-dimensional diagrams.

2.3. Molecular dynamic simulation studies

The molecular dynamics (MD) simulation at 100 ns confirmed the stability of the best-docked conformations of the drug and target among the six compounds. The simulation was conducted using the Desmond module of Schrodinger's suite (Merzouki *et al.*, 2023). Before the MD simulation, the protein and ligand in the best-docked complex underwent pre-processing. They were simulated at a temperature of 300 K and a pressure of 1.01325 bar, employing the NPT (constant number of particles, pressure, and temperature) ensemble for 100 ns. A salt concentration of 0.15 M NaCl was introduced to neutralize the system. The simulation trajectories of protein-ligand RMSD, RMSF, associated contacts, and protein structural information were analyzed using a simulation interaction diagram tool.

3. Results and discussion

3.1. ADMET properties analysis

ADMET modeling is gaining popularity in pharmaceutical research for its efficiency and cost-effectiveness. Table 1 presents the findings of applying Lipinski's rule of five (Merzouki *et al.*, 2023) (Molecular Weight < 500, Donor HB < 10, Acceptor HB < 10, and QPlogPo/w < 5) and Qikprop's ADMET prediction to all compounds (luteolin, 4-hydroxycinnamic acid, kaempferol, ferulic acid, citric acid, and quinic acid). These predictions demonstrate that the molecular weight, hydrogen bond donors, hydrogen bond donor acceptors, and expected octanol/water partition coefficient strictly adhere to Lipinski's rule of five, with no observed violations. The surface components of SASA, FOSA, FISA, PISA, and volume were predicted for all compounds, with values falling within the acceptable range specified in Schrödinger's Qikprop manual. The QPlogBB (predicted brain/blood partition coefficient) value was also within the acceptable range of -3.0 to +1.2. The QPPCaco (predicted apparent Caco-2 cell permeability) values greater than 500nm/sec indicated excellent permeability. Furthermore, all compounds showed high predicted qualitative human oral absorption HOA, except for quinic acid and citric acid, which had values below 25, indicating poor absorption.

Table 1. Lipinski's rule of five for all compounds and control compound

Compound Name	Molecular Weight	Donor HB	Acceptor HB	QPlogPo/w	Rule of five
Luteolin	286.240	3	4.5	0.984	0
Kaempferol	286.240	3	4.5	1.061	0
Quinic acid	192.168	5	7.85	-1.162	0
Ferulic acid	194.187	2	3.5	1.376	0
Citric acid	192.125	3	5.75	0.084	0
4-hydroxycinnamic acid	164.160	2	2.75	1.439	0
Erlotinib	393.441	1.5	7.4	4.487	0

Table 2 provides a detailed summary of the ADMET prediction for all compounds. Overall, the compounds displayed positive results for Lipinski's rule of five values and predicted ADMET pharmacokinetic parameters, with no observed violations in terms of drug characteristics. Additionally, the compounds exhibited drug-like characteristics as inhibitors of the epidermal growth factor receptor (EGFR) tyrosine kinase pathway, which is associated with causing cancer.

Table 2. ADMET analysis of in silico study for all compounds and control compound

Compound Name	SASA	FOSA	FISA	PISA	Volume	QPPCaco	QLogBB	HOA
Luteolin	502.6	0.000	250.1	252.4	841.86	42.02	-1.944	3
Kaempferol	506.5	0.000	238.9	267.6	845.22	53.75	-1.864	3
Quinic Acid	355.0	112.5	242.4	0.000	587.69	12.59	-1.507	2
Ferulic Acid	417.9	115.8	168.5	133.4	667.45	63.22	-1.177	3
Citric Acid	356.4	65.89	290.5	0.000	569.11	0.283	-2.029	1
4-Hydroxycinnamic Acid	378.8	23.79	169.3	185.7	588.93	62.21	-1.081	3
Erlotinib	763.2	394.5	35.94	332.7	1314.8	4519.1	-0.514	3

SASA = Solvent Accessible Surface Area. Range : 300.0–1000.0; FOSA = Hydrophobic Component of SASA. Range: 0.0–750.0; FISA = Hydrophilic Component of SASA. Range: 7.0–330.0; PISA = Pi Component of SASA. Range: 0.0–450.0; Volume = Total solvent-accessible volume in cubic angstroms. Range: 500.0 – 2000.0; QPPCaco = Predicted apparent Caco-2 cell permeability in nm/sec. Range: <25 poor, >500 excellent; QLogBB = Predicted brain/blood partition coefficient. Range: -3.0 – 1.2; HOA = Predicted qualitative human oral absorption. Range: 1, 2, or 3 for low, medium, or high

3.2. Molecular docking analysis

The term "molecular docking" pertains to using computational methods and algorithms to predict the binding interactions between a protein and a ligand molecule. This technique is employed in drug discovery and development to pinpoint possible drug candidates that can bind to a specific protein and alter its function (Naqvi *et al.*, 2018). The active site of protein EGFR (PDB: 4HJO) was targeted by lead compounds (Luteolin, 4-hydroxycinnamic acid, Kaempferol, ferulic acid, citric acid, and quinic acid) extracted from *Aristolochia longa*. These compounds were stable inside the cavity with significantly high energy values. The negative and low docking score values indicate that the compounds underwent strong and favorable binding interactions. Table 3 presents the evaluation of all compounds. The most stable compounds are luteolin, kaempferol, and quinic acid, with docking score values of -9.083 kcal/mol, -8.260 kcal/mol, and -5.857 kcal/mol, respectively. These values are higher than the control erlotinib of docking score value which is -5.101 kcal/mol. Fig. 3 shows that luteolin has a significantly higher binding energy than the control and interacts through four conventional hydrogen bonds with MET769, THR766, and ASP831. Additionally, residues ALA719, LEU834, LEU768, VAL702, LEU820, CYS773, and LEU693 are involved in hydrophobic interactions. As such, kaempferol also strongly binds to the protein's active site and stabilizes it through two conventional hydrogen bonds with MET769 and ASP831. Furthermore, residues VAL702, LEU834, ALA719, LEU820, LEU768, MET769, CYS773, and LEU694 are involved in its hydrophobic properties. While the in-silico studies have shown promising results regarding the potential of the compounds extracted from *Aristolochia longa* to inhibit the EGFR tyrosine kinase pathway, further investigations are required to determine their therapeutic efficacy in a clinical setting. Clinical trials involving human subjects are necessary to evaluate the compounds' safety, pharmacokinetics, and pharmacodynamics. In addition, *in vivo*, studies using animal models can provide insight into the compounds' efficacy and

potential side effects. Such investigations can aid in the development of effective therapies for cancer patients. It is also essential to evaluate the compounds' potential toxicity and long-term effects before they can be used in clinical practice. Therefore, extensive research is needed to establish the therapeutic potential of these compounds as an anticancer agent for treating the EGFR tyrosine kinase pathway.

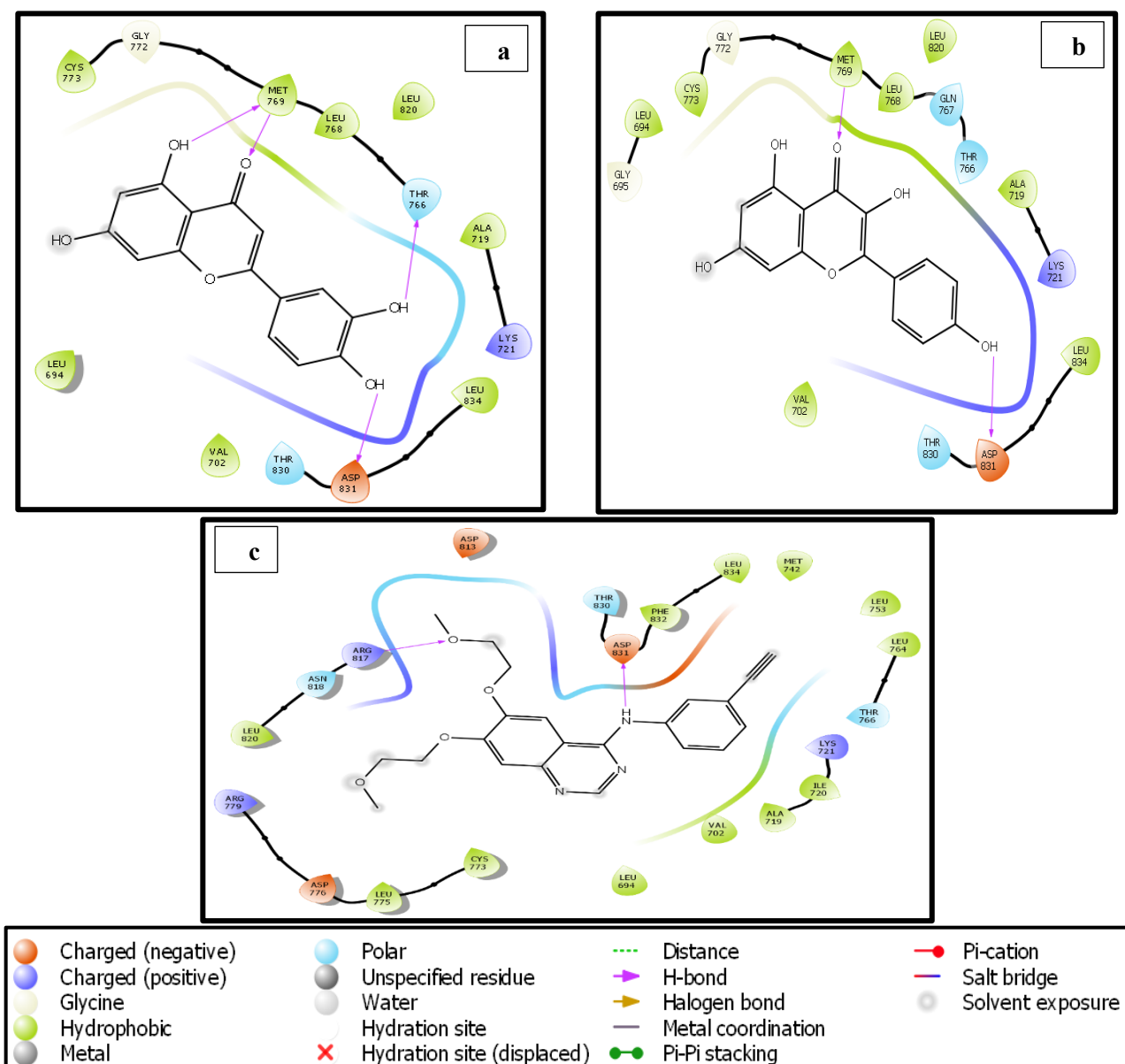


Fig. 3. The 2D intermolecular interactions of the best-docked complexes between (a) luteolin and the EGFR receptor, (b) kaempferol and the EGFR receptor and (c) between erlotinib (control) and the EGFR receptor.

3.1. Molecular dynamics simulation

MD simulations are computational techniques used to study the movement and behavior of atoms and molecules over time. They simulate the laws of physics to calculate particle trajectories and interactions. MD simulations provide insights into dynamics, thermodynamics, and structural properties by solving equations of motion. The research examined molecular dynamics simulations to assess the Root Mean Square Deviation (RMSD) of the protein (on the left Y-axis) and the ligand (on the right Y-axis). Additionally, it measured the Root Mean Square Fluctuation (RMSF) and the protein-ligand contacts for the top docking outcome involving luteolin and the EGFR receptor.

Table 3. The molecular docking studies of selected compounds against EGFR (PDB: 4HJO) using XP docking

Compound name	Dock Score	Interacting residues	Type of Bond
Luteolin	-9.083	2*MET769	Hydrogen bond
		THR766	Hydrogen bond
		ASP831	Hydrogen bond
Kaempferol	-8.260	MET769	Hydrogen bond
		ASP831	Hydrogen bond
		2*ASP813	Hydrogen bond
Quinic acid	-5.857	ARG817	Hydrogen bond
		ASN818	Hydrogen bond
		ASP831	Hydrogen bond
		LYS721	Salt bgridge
Ferulic acid	-4.655	MET769	Hydrogen bond
		ASP831	Hydrogen bond
		ARG817	Hydrogen bond
		ASN818	Hydrogen bond
Citric acid	-4.424	LYS721	Hydrogen bond
		PHE699	Hydrogen bond
		2*LYS721	Salt bgridge
		ARG817	Salt bgridge
4-hydroxycinnamic acid	-3.854	THR766	Hydrogen bond
		CYS773	Hydrogen bond
Erlotinib	-5.101	ASP831	Hydrogen bond
		ARG817	Hydrogen bond

Fig. 4 plots the RMSD scores for the C-alpha atoms over time. The RMSD plot for the Luteolin-EGFR complex demonstrates stability up to twenty nanoseconds. It is common for small globular proteins to exhibit changes in RMSD values within the range of 1-3 Å, indicating a balanced protein structure.

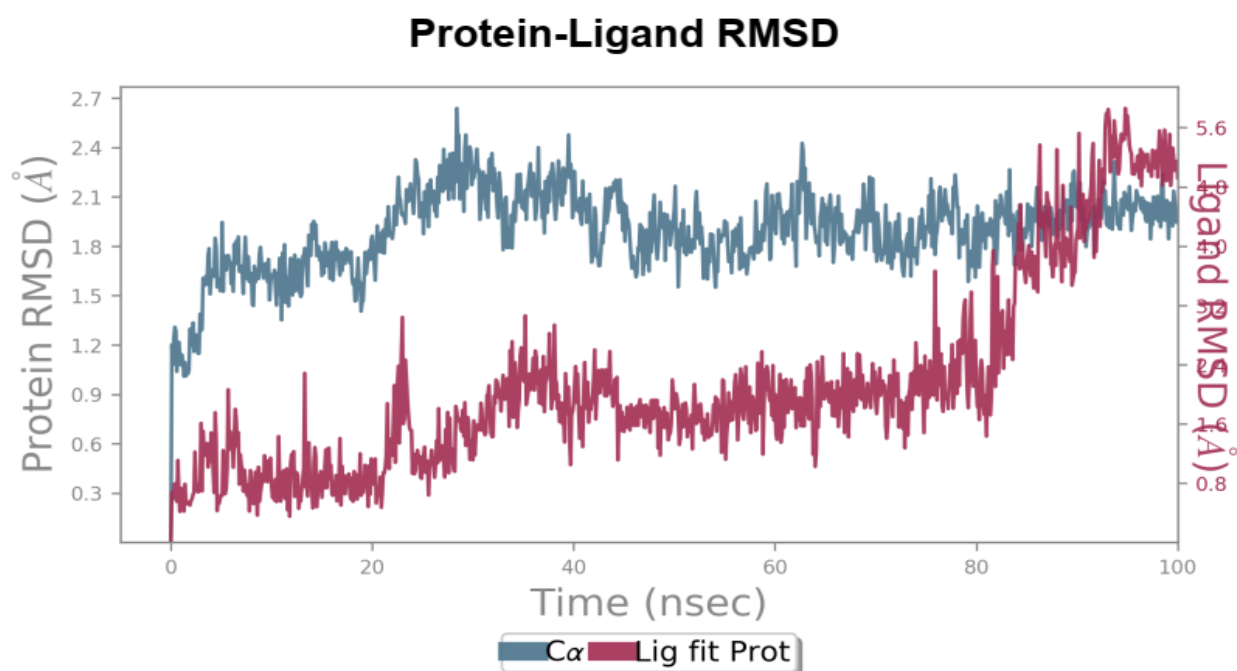


Fig. 4. RMSD (Root mean square deviation) of the C-alpha atoms of protein and the ligand with time (luteolin-EGFR).

However, larger proteins may display a wider range of RMSD values, which suggests that the protein is appropriately balanced and shows an ideal ligand-receptor binding during the simulation. At eighty nanoseconds, a sudden rise in the RMSD score of the Luteolin ligand was observed, indicating a change in the ligand binding mode. In [Fig. 5](#), The root mean square fluctuation (RMSF) was utilized to detect significant fluctuations in the protein domain. For the Luteolin-EGFR complex, the RMSF values ranged from 0.5 to 2 Å, except for the terminal amino acid residues. It was observed that the tails (N- and C-terminal) of the protein exhibited higher fluctuations compared to other parts. Typically, secondary structure elements such as alpha helices and beta strands are more rigid than the unstructured regions of the protein. As a result, they tend to fluctuate less than the loop regions. Results of MD shed light on the fact that Hydrogen Bonds, Hydrophobic, Ionic and Water Bridges interactions are the predominant ligand-receptor interaction, as shown in [Figs. 6](#).

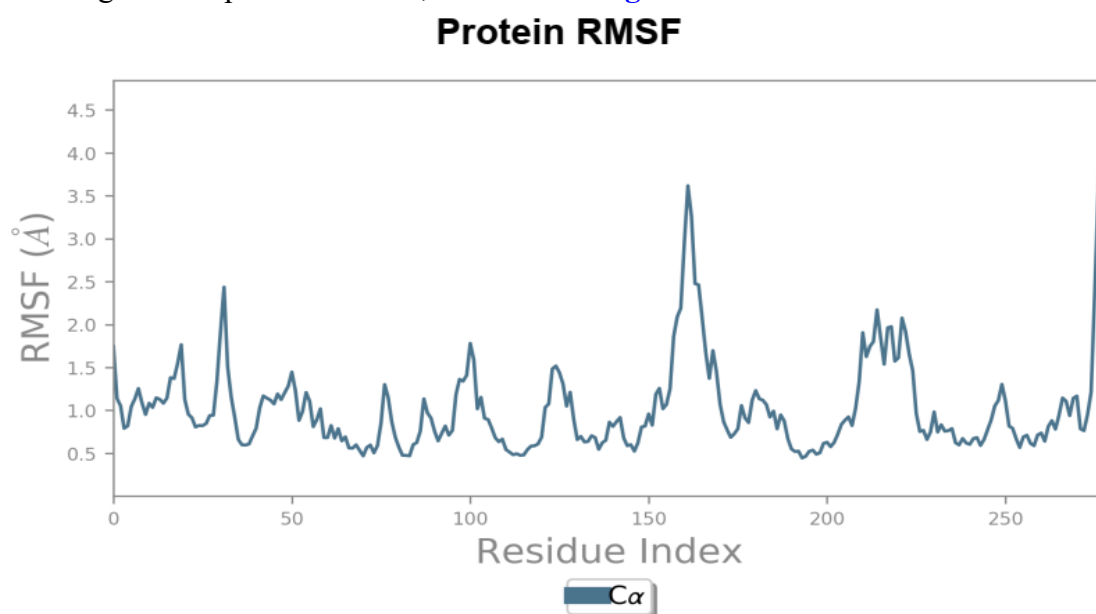


Fig. 5. Residue-wise RMSF (Root Mean Square Fluctuation) of protein (Luteolin-EGFR).

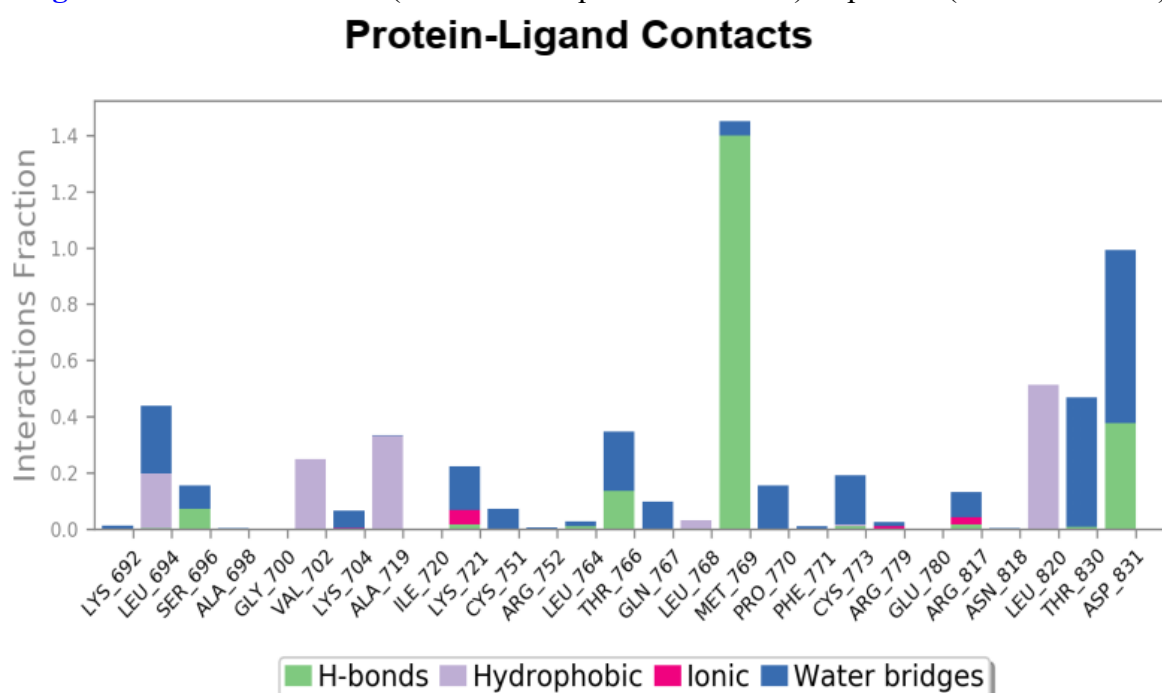


Fig. 6. Protein-ligand contact histogram (Luteolin-EGFR).

MET766, THR769 and ASP831 significantly consider H-bonds for the luteolin-EGFR complex. Some residues made significant strong hydrophobic interactions GLY702, LYS719 and LEU820. The obtained outcomes exhibit concurrence and consistency with the predictions generated through molecular docking. This indicates a correspondence between computational findings, the preferred binding orientations, and interactions predicted between the ligand and receptor in the study context. It's important to note that molecular docking and MD simulation is a predictive tool and although it can provide valuable insights, it's not infallible. Careful validation and further experimental studies are often necessary to confirm the results and fully understand the underlying mechanisms.

Conclusion

Numerous initiatives and research endeavors are currently underway in the field of drug screening against the inactive EGFR tyrosine kinase domain complexed with Erlotinib (PDB: 4HJO), presenting a global challenge in predicting the binding of drugs to specific targets for cancer treatment. This study utilized a rigorous computational workflow to predict the binding potential of five natural compounds (Luteolin, 4-hydroxycinnamic acid, Kaempferol, ferulic acid, citric acid, and quinic acid) extracted from *Aristolochia longa* towards the EGFR target, comparing it with the binding of the control erlotinib to its designated target. Among these five compounds, three potential EGFR inhibitors exhibited notable binding capabilities compared to the control erlotinib. Notably, Luteolin, Kaempferol, and quinic acid demonstrated higher binding energies than the reference molecule, with binding affinities of -9.083 kcal/mol, -8.260 kcal/mol, and -5.857 kcal/mol, respectively, indicating a favorable binding affinity to the active site. Various techniques, including Lipinski's rule of five and ADMET parameters, were employed to evaluate the pharmacological characteristics of these natural compounds. Molecular dynamics simulations, encompassing analysis of RMSD, RMSF, and hydrogen bond interactions, confirmed the stability and favorable interaction of the most effective compound with the EGFR protein. This study underscores the *in-silico* potential of compounds derived from aromatic and medicinal plants against the EGFR tyrosine kinase domain, suggesting their suitability for further in vitro and in vivo assessments and potential therapeutic application in the recovery of cancer patients.

Disclosure statement: *Conflict of Interest:* The authors declare no conflicts of interest.

Compliance with Ethical Standards: This article contains no studies involving human or animal subjects.

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