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Computational analysis identifies withastramonolide and kaempferol as highly potent compounds from *Datura stramonium* targeting EGFR-TK in non-small cell lung cancer (NSCLC)

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Abstract
Epidermal Growth Factor Receptor (EGFR) is a key player in cancer progression, influencing critical signaling pathways such as Wnt/β-catenin, Transforming Growth Factor (TGF-β), and Phosphoinositide-3-Kinase (PI3K). Despite EGFR inhibitors in cancer treatment, genetic mutations lead to persistent activation and resistance, highlighting the urgent need for new therapeutic approaches. In this study, the anticancer potential of *Datura stramonium* was explored through computational approaches. A total of 50 compounds from *Datura stramonium* were sourced using the IMPPAT database, followed by ADMET predictions, drug-likeness assessments, and molecular docking using Vina-GPU-2.0. Of these, 15 compounds met the necessary criteria, with Withastramonolide and Kaempferol demonstrating significant binding affinity to the catalytic residues of EGFR-TK, surpassing the reference inhibitor erlotinib. The binding energies for Withastramonolide and Kaempferol were -9.2 kcal/mol and -8.3 kcal/mol, respectively, compared to the reference compound's -7.0 kcal/mol. Molecular dynamics simulations conducted over a 100 ns trajectory for CID-21607602 and CID-5280863 further validated the stability of these complexes, with interaction energies of -133.211 kJ/mol and -101.422 kJ/mol. These findings suggest that phytocompounds from *Datura stramonium* may serve as potent inhibitors of EGFR-TK, offering promising therapeutic potential for the treatment of various cancers.

Keywords: EGFR-TK, *Datura stramonium*, molecular docking, molecular dynamics, cancer therapy, withastramonolide, kaempferol

Introduction

Cancer encompasses a range of diseases characterized by the unregulated proliferation and dissemination of abnormal cells, which, if left untreated, can lead to fatal outcomes. (Beale *et al*., 2010) [6] Cancer remains a significant global health issue, with over ten million new cases diagnosed annually. Approximately half of these cases occur in developed nations, and the disease is responsible for more than six million deaths each year. (Aboul-Fadl *et al*., 2012) [1] According to the World Health Organization (WHO), the most prevalent types of cancer among men include lung, prostate, colorectal, stomach, and liver cancers, while breast, colorectal, lung, cervical, and thyroid cancers are most common among women. Research has identified approximately 1,000 distinct agents with the potential to induce cancer. (Bray *et al*., 2018; Wolf *et al*., 2023) [9, 29] Among various types of cancer, lung cancer is the most common among men. The Epidermal Growth Factor Receptor (EGFR) is frequently expressed in non-small cell lung cancer (NSCLC) (Wang *et al*., 2021) [28]. Activation of EGFR modulates cellular signal transduction networks to control cell growth and proliferation. The tyrosine kinase domain of EGFR, referred to as 1M17, is essential for initiating intracellular signaling and regulating cell growth signals. (Solassol *et al*., 2019) [24] Excessive activation of EGFR can lead to uncontrolled cell proliferation, making targeted therapies that inhibit EGFR tyrosine kinase activity particularly valuable in cancer treatment (Reddy *et al*., 2018) [23]. Drugs that block EGFR proteins, such as gefitinib and erlotinib, have led to extensive clinical trials involving patients with advanced-stage lung cancer. These inhibitors are used to counteract the effects of EGFR activation, which promotes cellular growth, proliferation, invasion, and metastasis, and inhibits apoptosis, thereby contributing to the progression of cancers such as NSCLC (Chaft *et al*., 2021) [11]. *Datura stramonium* L., commonly known as Thorn Apple or Jimson Weed, is an annual herb from the Solanaceae family that is widely recognized for its medicinal properties. Traditionally utilized in the Indian subcontinent for treating various ailments such as asthma, sinus infections, rheumatism, and pain, *D. stramonium* has demonstrated several therapeutic properties, including anti-inflammatory, antiasthmatic, and antioxidant activities (Alum *et al*., 2023) [4]. The plant is a rich source of tropane alkaloids, including the anticholinergic drugs atropine and scopolamine, and contains other active phytochemical constituents such as flavonoids, terpenoids, steroids, withanolides, glycosides, saponins, tannins, and carbohydrates (Alper & Cennet, 2022) [3].

Molecular docking is a fundamental technique in structural molecular biology and computer-aided drug design (Srivastava *et al*., 2010) [25]. In this study, AutoDock was employed to analyze the binding orientations and predict the binding affinities of phytochemical compounds derived from *Datura stramonium* (Ajeet & Kumar, 2013) [2]. This approach provides insights into how two molecules, such as drugs and enzyme receptors, align and interact to achieve stable binding (Dash & Kashyap, 1991) [13]. Recent studies, such as those by Ahmad *et al*. (2009), have shown that aqueous leaf extracts of *Datura stramonium* exhibit cytotoxic effects against various cancer cell lines, including head and neck, breast, and lung cancers. The current study aims to explore molecular modeling and docking studies of *Datura stramonium* phytochemical Withastramonolide analogs about EGFR proteins. Given the role of EGFR in cancer progression, understanding how these phytochemical analogs interact with EGFR could provide insights into novel therapeutic strategies for combating EGFR-driven cancers.

Materials and methodology

Phytocompounds library prepration

Data was collected from scientific literature and various databases, including IMPPAT, to develop a library comprising 50 unique compounds derived from *Datura stramonium* for the purpose of screening anti-cancer agents targeting the Epidermal Growth Factor Receptor Tyrosine Kinase (EGFR-TK). (Karthikeyan *et al*., 2018) [16]. This library was meticulously assembled by selecting compounds with known three-dimensional (3D) structures, as documented in PubChem (https://pubchem.ncbi.nlm.nih.gov) (Kim *et al*., 2016) [17].

Ligand preparation

The reference molecule Erlotinib (AQ4, CID: 176870) was retrieved from PubChem in SDF format, and co-crystallized with the protein. Three-dimensional structures of *Datura stramonium* compounds were also obtained from online sources and databases, including PubChem, in SDF format. Both the reference molecule and ligand compounds were converted to PDB format using Open Babel software (version 2.3.1), following the method by O'Boyle *et al*. (2011) [20]. AutoDockTools, as described by Morris *et al*. (2009) [19], were then used to convert the compounds into pdbqt format for further analysis.

Receptor preparation

For the analysis, the crystal structure of the Epidermal Growth Factor Receptor (PDB ID: 1M17) was acquired from the RCSB Protein Data Bank (https://www.rcsb.org) (Berman *et al*., 2000) [7]. The 1M17 protein, consisting of a single chain with a sequence length of 333 amino acids, forms a complex with a specific ligand, AQ4 [6,7-BIS(2-METHOXY-ETHOXY)QUINAZOLINE-4-YL]-(3-ETHYNYLPHENYL)AMINE. To concentrate on the pertinent components, nonspecific water molecules and ions were removed using PyMOL software. The cleaned protein structure was then saved in PDB format to facilitate subsequent analysis.

Molecular interaction analysis

Ligplot+ v.2.2.5 software was employed to visualize the molecular interactions, specifically hydrogen bonds and hydrophobic interactions, within the protein-ligand complexes. Additionally, Biovia Discovery Studio Visualizer 2022 was used to generate both 3D and 2D representations of the top compounds, which exhibited the lowest binding energies with EGFR-TK. This facilitated a detailed analysis of the interactions within the complexes. [https://discover.3ds.com/discovery-studio-visualizer-download] (Biovia, 2017; Wallace *et al*., 1995) [8, 27].

Drug likeness and toxicity prediction

The Lipinski rule of five is a key criterion for evaluating drug-likeness. It states that a compound should have no more than five hydrogen bond donors, no more than ten hydrogen bond acceptors, a molecular weight under 500, and a cLogP value of 5 or lower to ensure optimal absorption and permeability. On other hands, SwissADME was utilized for the in-silico evaluation of drug-likeness and toxicity of the proposed ligands. It offers insights into the compounds drug-likeness, physicochemical properties, pharmacokinetics, lipophilicity, water solubility, medicinal chemistry. AdmetSAR assesses potential risks such as mutagenicity, tumorigenicity, irritation, and reproductive toxicity, while also offering parameters like molecular weight, consensus lipophilicity (cLogP), total polar surface area (TPSA), solubility, drug-likeness, and drug score. Drug-likeness indicates the likelihood of a substance being an orally active drug (Cheng *et al*., 2012).

Molecular dynamics simulations

Molecular dynamics simulations were performed to validate docking analysis results and assess structural modifications in Epidermal Growth Factor Receptor Tyrosine Kinase (EGFR-TK) and its associated protein-ligand complexes. These simulations were executed using GROMACS 2022.4 on an Ubuntu 16.04 LTS (64-bit) system, equipped with 4 GB of RAM and an Intel Core i5-6400 CPU. The CHARMM36 force field (Vanommeslaeghe *et al*., 2010) was applied to generate structural configurations for both the proteins and the protein-ligand complexes.The systems were first solvated using the TIP3P water model, employing dodecahedral periodic boundary conditions to establish the simulation box dimensions. Water molecules were introduced based on the method outlined by Izadi and Onufriev (2016). To neutralize the system at 300 K, sodium (Na^+) and chloride (Cl^-) ions were added. Energy minimization, under periodic boundary conditions, was achieved using the Particle Mesh Ewald (PME) method and a Verlet cutoff scheme set at 10 kJ/mol, with 50,000 steps of steepest descent optimization.After minimization, the system underwent equilibration through NVT (constant temperature) and NPT (constant pressure) phases, maintaining a temperature of 300 K and pressure of 1.0 atm, respectively. The Parrinello-Rahman method, with a time step of 2 fs, was used to regulate the system pressure. Once the final configurations of the most promising compounds were obtained from the NPT equilibration, a 100 ns production run was conducted to offer comprehensive insights into system dynamics (Gupta *et al*., 2021; Prasanth *et al*., 2021).

Results

Molecular Docking and Interaction Visualization

Molecular docking is a critical technique in drug discovery, enabling the prediction of how ligands bind and orient themselves within specific receptor sites. The Docking Score, which reflects binding strengths, indicates that lower binding energies signify a stronger affinity between the target protein and the ligands (Calixto, 2019; Daoui *et al*., 2021) [10, 12]. In this study, the docking process was validated by re-docking the reference ligand into the EGFR (ID-1M17) protein crystal structure, confirming precision and reliability with a binding energy of -7.0 kcal/mol. A thorough comparison of the docked reference molecule AQ4 with the co-crystallized reference in the crystal structure, as depicted in Figure 1, affirmed their alignment.

Among 50 phytocompounds screened, two exhibited binding energies between -9.2 kcal/mol and -8.3 kcal/mol, which are lower than the binding energy of the reference molecule AQ4 (-7.0 kcal/mol) as shown in Table 1. From these, two compounds—Withastramonolide and Kaempferol—demonstrated favorable interactions and were selected for further investigation, with binding energies of -9.2 kcal/mol and -8.3 kcal/mol, respectively.

Interactions between ligands and specific amino acid residues at the protein's active site are crucial for

determining binding affinity and efficacy (Daoui *et al*., 2021) [12]. The predominant interactions observed in this study were hydrophobic interactions and hydrogen bonding (Baig *et al*., 2020) [5]. Biovia Discovery Studio 2020 and LigPlot+ v.2.2.5 were employed for 3D and 2D visualization of these interactions, as illustrated in Figure 3. The reference molecule AQ4 formed a single hydrogen bond with Met769 (2.70 Å) and established nine hydrophobic interactions with residues including Ala719, Gln767, Leu764, Lys721, Gly695, Val702, Thr830, Asp831, Leu768, Gly762, Phe771, Pro770, Met742, and Glu738, with a binding energy of -7.0 kcal/mol.

Withastramonolide, the top-screened phytocompound, exhibited the highest binding affinity at -9.2 kcal/mol. It formed five hydrogen bonds with Asp831, Cys773, Met769, Thr830, and Asp831, at bond lengths of 3.19 Å, 2.80 Å, 3.16 Å, 2.83 Å, and 3.07 Å, respectively. Additionally, it engaged in hydrophobic interactions with Leu694, Gly772, Ala719, Leu820, Lys721, Thr760, and Asp776.Kaempferol, another notable compound, displayed a binding energy of -8.3 kcal/mol with EGFR. It formed four hydrogen bonds with Lys721, Asp831, Ala719, and Thr830, at distances of 3.22 Å, 3.00 Å, 2.92 Å, and 2.96 Å, respectively, and engaged in eight hydrophobic interactions with Met742, Ile765, Thr766, Ile720, Val702, Leu764, and Gly772.These findings underscore the potential of Withastramonolide and Kaempferol as promising candidates for further drug development targeting EGFR, based on their strong binding affinities and interaction profiles.

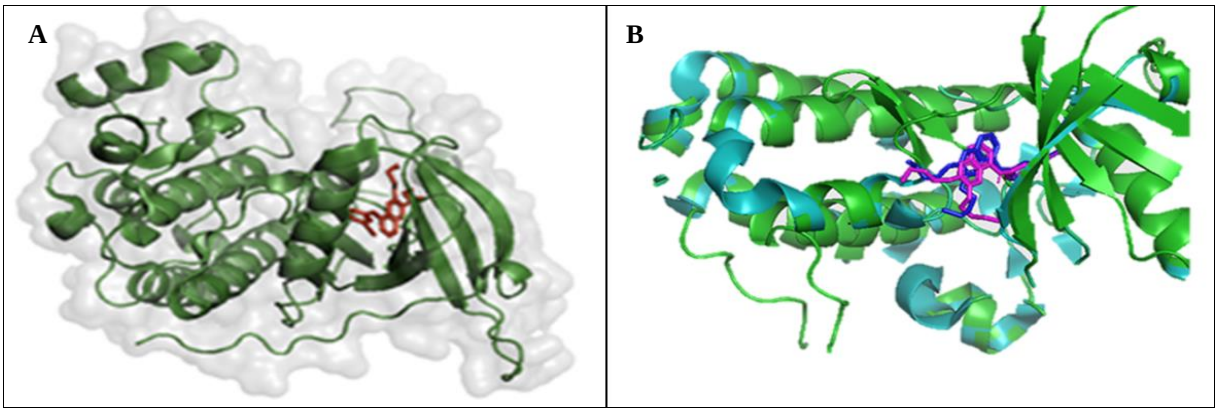

Fig 1: (A) 3D Structure of Protein (1M17) (B) Superimposition of experimental reference (AQ4) in Blue color and docked reference (AQ4) in Pink color with 3D structure of protein 1M17.

Table 1: Top hit compounds with their CID No and binding energy scores.

S. No	Compounds Name	CID No	Binding Scores
1.	Reference (Erlotinib)	176870	-7.0
2.	Withametelin F	71718234	-9.8
3.	Withanolide D	161671	-9.7
4.	Withastramonolide	21607602	-9.2
5.	Quercetin	5280343	-8.6
6.	Kaempferol	5280863	-8.3
7.	Chrysin	5281607	-8.3
8.	Daturalactone	21607604	-8.3

Table 2: Drug-Likeness Prediction of Phytocompounds, Computed by SwissADME

S. No	Formula	Mol.wt (g/mol)	NHD	NHA	NRB	TPSA (A^{02})	LogP	Lipinski Rule of Five Violation
1.	$C_{22}H_{23}N_3O_4$ (Reference)	393.44	1	3	10	74.73	3.48	Yes, 0 violation
2.	$C_{28}H_{38}O_7$	486.60	3	7	3	116.59	2.59	Yes, 0 violation
3.	$C_{15}H_{10}O_6$	286.05	4	6	1	111.13	2.65	Yes, 0 violation

Table 3: ADME Predictions of Phytocompounds, Computed by Swiss ADME

S. No	Phytocompounds name	Log Kp cm/s	GI Absorption	BBB Permeability	Inhibitor Interaction (Swiss ADME)					
					P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
1.	Reference (AQ4)	-6.35	High	Yes	No	Yes	Yes	Yes	Yes	Yes
2.	Withastramo-nolide	-7.41	High	No	Yes	No	No	No	No	No
3.	Kaempferol	-6.70	High	No	No	Yes	No	No	Yes	Yes

Table 4: Toxicological characteristics of the screened phytocompounds admetSAR webserver

S. No	Phytocompounds Name	Carcinogenicity	AMES Toxicity	Rat Acute toxicity LD50, mol/kg
1.	Erlotinib	Non-carcinogenic	Non-AMES toxic	2.5379
2.	Withastramonolide	Non-carcinogenic (0.204)	Non-AMES toxic (0.434)	0.189
3.	Kaempferol	Non-carcinogenic (0.716)	Non-AMES toxic (0.546)	0.488

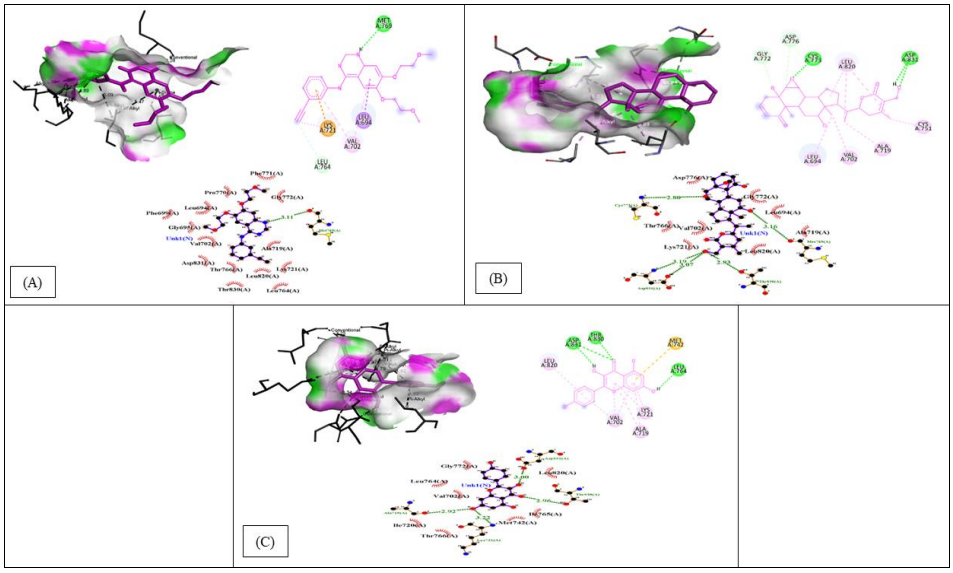

Fig 2: Representation of 3D and 2D interactions of reference and top screened phytocompounds complexes. (A) Reference AQ4, (B) Withastramonolide (C) Kaempferol.

Molecular dynamics simulation

After completing the docking studies, molecular dynamics simulations were executed. This evaluation involved the EGFR protein-reference complex along with the docked ligand complexes of the primary 2 phytocompounds (Withastramonolide, Kaempferol). To accomplish this, a 100 ns molecular dynamics (MD) simulation was performed. Various parameters, such as Root Mean Square Deviation (RMSD), Root Mean Square Fluctuations (RMSF), Hydrogen Bonds (Hb), Radius of Gyration (Rg), and interaction energy, were calculated based on the MD trajectories. The outcomes obtained from these calculations were graphically illustrated for analysis purposes using xmgrace, showcased in Figures 3.

RMSD (System stability and flexibility)

Root Mean Square Deviation (RMSD) is used to assess the stability of biological molecules by tracking structural changes over time. In a 100 ns molecular dynamics simulation, the RMSD values of the native protein and protein-ligand complexes, including EGFR complexes with Withastramonolide and Kaempferol, were analyzed. The results showed RMSD values of 1.026 nm for the native protein, 1.020 nm for the reference ligand, and 1.041 nm and 1.170 nm for the respective complexes. While the EGFR-Withastramonolide complex exhibited instability after 5 nanoseconds, the EGFR-Kaempferol complex remained more stable. Overall, the RMSD analysis confirmed the stability of the protein-ligand complexes throughout the simulation.

RMSF

In this study, we explored the positional changes of individual protein elements in their natural form and when interacting with specific ligands (Baildya *et al*., 2021) [] (Rawat *et al*., 2024) [22]. Within proteins, segments like loops, turns, and coils exhibited higher RMS fluctuations compared to helices and sheet structures. The RMSF plots in Figure 3B illustrate the variations for EGFR, the reference, and all protein-ligand combinations. The mean RMSF values for the protein, reference complex, Withastramonolide-EGFR, and Kaempferol-EGFR were measured at 0.267, 0.187, 0.348 and 0.378 nm correspondingly, detailed in Table 5.

Radius of Gyration

The Radius of Gyration (Rg) measures the compactness of a system, with consistent Rg values indicating stable protein-ligand complexes and proper protein folding. Fluctuations in Rg suggest protein unfolding or instability. For the 1M17 protein, the average Rg values were 1.838±0.019 nm for the native protein and 0.187±0.122 nm for the 1M17-reference complex. The Withastramonolide-EGFR and Kaempferol-EGFR complexes had Rg values of 1.791±0.020 nm and 1.844±0.037 nm, respectively. Minor variations in Rg indicate the stability of these protein-ligand interactions.

Hydrogen Bonds

The stability of protein-ligand complexes is influenced by interactions such as hydrogen bonds, hydrophobic interactions, and electrostatic forces. Figure 3D charts the number of hydrogen bonds formed during the 100 ns simulation for each complex. Both the Withastramonolide-EGFR and Kaempferol-EGFR complexes exhibited five hydrogen bonds. These hydrogen bonds, established in all simulated complexes with the 1M17 protein, highlight their critical role in maintaining the stability of the complexes.

Interaction Energy Calculations

The free interaction energies of the EGFR-ligand complexes were evaluated using the Parrinello-Rahman parameter in GROMACS. The average interaction energies across all complexes fell within the acceptable range of -90 to -200 kJ/mol. During the 100 ns molecular dynamics simulation, the EGFR-Withastramonolide complex exhibited the highest interaction energy at -133.211kJ/mol, followed by EGFR-Kaempferol at -101.422 kJ/mol. All the values were lower than the interaction energy of the reference molecule, which was recorded at -163.717 kJ/mol (see Table 5). As illustrated in Figure, the interaction energy plot for all protein-ligand complexes remained consistently within the acceptable range throughout the simulation. These interaction energy findings strongly support the molecular docking results, reinforcing the high affinity of the top phytocompounds for EGFR.

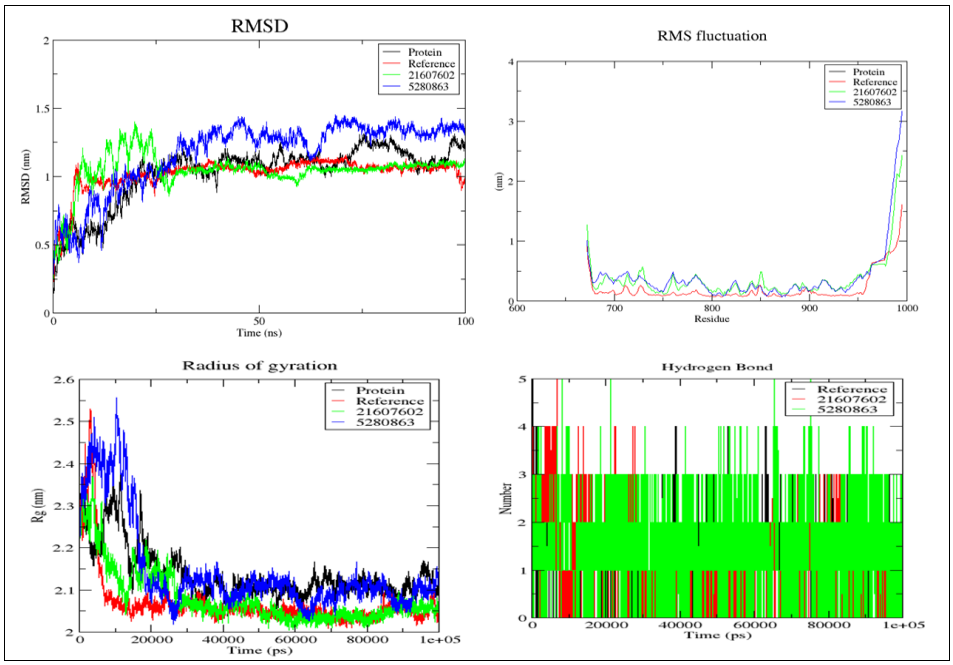

Fig 3: A plot showing (A) RMSD (B) RMS fluctuation (C) Radius of gyration (D) Hydrogen bond

Table 5: The average values of RMSD, RMSF, RG, H-bond, and Interaction energy

S. No	Complexes	Average RMSD (nm)	Average RMSF (nm)	Average RG (nm)	H-bond	Interaction energy (kJ/mol)
1.	1M17 (Protein)	1.026±0.160	0.267±0.158	1.838±0.019		—
2.	1M17-Reference	1.020±0.072	0.187±0.122	1.781±0.020	4	-163.717
3.	1M17- Withastramonolide	1.041±0.076	0.348±0.180	1.791±0.020	5	-133.211
4.	1M17- Kaempferol	1.170±0.200	0.378±0.218	1.844±0.037	4	-101.422

Discussion

Cancer remains a critical global health challenge, with substantial advancements in research over the past decade. The limitations of current chemotherapies—such as adverse effects and resistance—highlight the urgent need for more effective and less toxic anticancer agents. Our study employed molecular docking and dynamics simulations to identify four potent phytochemicals from *Datura stramonium*, which exhibited superior binding affinity to EGFR-TK compared to other tested compounds. We evaluated 15 compounds using drug-likeness filters, focusing on criteria such as blood-brain barrier penetration and adherence to Lipinski's Rule of Five, identifying promising candidates for further analysis. The study underscores the value of medicinal plants and their derivatives in drug development, with approximately 35% of modern pharmaceuticals originating from natural sources. The selected phytochemicals demonstrated significant anticancer activity by inducing oxidative stress, inhibiting key signaling pathways (PI3K/Akt, MAPK), and downregulating HIF-1 to impede angiogenesis. Molecular docking and pharmacokinetic profiling on platforms such as SwissADME validated these compounds as potential EGFR-TK inhibitors. Erlotinib (AQ4), used as a reference, showed a binding energy of -7.0 kcal/mol and formed hydrophobic interactions with several residues within the EGFR-TK active site, alongside a hydrogen bond with Met769. The top candidate, Withastramonolide (PubChem ID −21607602), demonstrated the highest binding affinity at -9.2 kcal/mol, with hydrogen bonds to residues including Asp831, Cys773, Met769, Thr830, and Asp83. Kaempferol (PubChem ID 5280863) also showed promising results with a binding score of -8.3 kcal/mol and hydrogen bonds with Lys721, Asp831, Ala719, and Thr830. A 100-ns molecular dynamics simulation confirmed the stability of these protein-ligand interactions. The analysis of molecular dynamics trajectories, including RMSD, RMSF, Rg, H-Bond, and interaction energies, revealed notable stability throughout the simulation period. These findings suggest that the identified phytochemicals are promising candidates for further drug development targeting EGFR-TK.

Conclusion

In the present study, a comprehensive set of in silico techniques, including molecular docking, and molecular dynamics simulations, were employed. to validate the docking and simulation outcomes, with the primary objective of identifying potential phytochemicals from *Datura stramonium* against EGFRK-TK. Thus, the two predicted lead candidates were expected to be favourable and promising compounds addressing the EGFR-TK anticancer goal. As a result, the approaches used in this research might be used and investigated as a benchmark for current drug development procedures in the next years. Furthermore, the results would make a substantial contribution to the development of novel methodologies for identifying anticancer medicines, as well as the identification and optimisation of drug-like leads.

Declaration of competing interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

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Author contribution: P.P wrote the manuscript and done all experiments parts. P.J analyzed and interpreted data. S.R draw Ligplots. S. C. conceptualized and supervised the study. The whole manuscript was approved by all authors.

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Reference

1. Aboul-Fadl T, Radwan AA, Attia MI, Al-Dhfyan A, Abdel-Aziz HA. Schiff bases of indoline-2,3-dione (isatin) with potential antiproliferative activity. Chem Cent J,2012:6(1):49. doi:10.1186/1752-153X-6-49.
2. Ajeet TL, Kumar P. Designing of novel 6(H)-1,3,4-thiadiazine derivatives as MMP12 inhibitors: A MLR and docking approach. Am J Pharm Sci,2013:1(2):29-34.
3. Alper M, Cennet Ö. Antioxidant activity and phenolic composition of ethanol extracts of Momordica charantia and *Datura stramonium*. Kahramanmaraş Sütçü İmam Üniversitesi Tarım ve Doğa Dergisi,2022:25(1):1-9.
4. Alum EU, Famurewa AC, Orji OU, Aja PM, Nwite F, Ohuche SE, *et al*. Nephroprotective effects of *Datura stramonium* leaves against methotrexate nephrotoxicity via attenuation of oxidative stress-mediated inflammation and apoptosis in rats. Avicenna J Phytomed,2023:13(4):377.
5. Baig MW, Nasir B, Waseem D, Majid M, Khan MZI, Haq I. Withametelin: A biologically active withanolide in cancer, inflammation, pain and depression. Saudi Pharm J,2020:28(12):1526-37.
6. Beale JM, Block J, Hill R. Organic medicinal and pharmaceutical chemistry. Philadelphia: Lippincott Williams & Wilkins, 2010. Available from: https://alraziuni.edu.ye/uploads/pdf/ORGANIC-MEDICINAL-AND-PHARMACEUTICAL-CHEMISTRY.pdf.
7. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, *et al*. The protein data bank. Nucleic Acids Res,2000:28(1):235-42.
8. Biovia DS. Discovery studio modeling environment. Release, 2017.
9. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin,2018:68(6):394-424. doi:10.3322/caac.21492.
10. Calixto JB. The role of natural products in modern drug discovery. Anais da Academia Brasileira de Ciências, 2019, 91.
11. Chaft JE, Rimner A, Weder W, Azzoli CG, Kris MG, Cascone T. Evolution of systemic therapy for stages I–III non-metastatic non-small-cell lung cancer. Nat Rev Clin Oncol,2021:18(9):547-57.
12. Daoui O, Elkhattabi S, Chtita S, Elkhalabi R, Zgou H, Benjelloun AT. QSAR, molecular docking and ADMET properties in silico studies of novel 4,5,6,7-tetrahydrobenzo [D]-thiazol-2-Yl derivatives derived from dimedone as potent anti-tumor agents through inhibition of C-Met receptor tyrosine kinase. Heliyon, 2021, 7(7). doi:10.1016/j.heliyon.2021.e07518.
13. Dash B, Kashyap L. Five specialized therapies of Ayurveda, Panchakarma: Based on Ayurveda. New Delhi: Concept Publishing Company, 1991.
14. Gioia D, Bertazzo M, Recanatini M, Masetti M, Cavalli A. Dynamic docking: A paradigm shift in computational drug discovery. Molecules,2017:22(11):2029.
15. Joshi P, Pandey P, Rawat S, Chandra S. Repurposing of Drug Bank compounds against Plasmodium falciparum dihydroorotate dehydrogenase as novel anti-malarial drug candidates by computational approaches. In Silico Pharmacol,2024:12(2):60. doi:10.1007/s40203-024-00232-1.
16. Karthikeyan M, Karthikeyan BS, Vivek-Ananth RP, Chand RB, Aparna SR, Pattulingam M, *et al*. IMPPAT: A curated database of Indian medicinal plants, phytochemistry and therapeutics. Sci Rep,2018:8(1):1-9. doi:10.1038/s41598-018-26795-3.
17. Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, *et al*. PubChem substance and compound databases. Nucleic Acids Res, 2016, 44(D1).
18. Lipinski CA. Lead-and drug-like compounds: The rule-of-five revolution. Drug Discov Today Technol,2004:1(4):337-41.
19. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, *et al*. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem,2009:30(16):2785-91. doi:10.1002/jcc.21256.
20. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An open chemical toolbox. J Cheminformatics,2011:3(1):33. doi:10.1186/1758-2946-3-33.
21. Oshima Y, Bagchi A, Hikino H, Sinha SC, Sahai M, Ray AB. Withametelin, a hexacyclic withanolide of Datura metel. Tetrahedron Lett,1987:28(18):2025-7.
22. Rawat S, Pandey P, Joshi P, Bisht A, Arya V, Maiti P, *et al*. Exploring the molecular mechanism of anti-inflammatory action of Coriandrum sativum using network pharmacology, molecular dynamic simulation, and density functional theory. J Proteins Proteomics, 2024: doi:10.1007/s42485-024-00163-7.
23. Reddy PS, Lokhande KB, Nagar S, Reddy VD, Murthy PS, Swamy KV. Molecular modeling, docking, dynamics and simulation of gefitinib and its derivatives with EGFR in non-small cell lung cancer. Curr Comput Aided Drug Des,2018:14(3):246-52.
24. Solassol I, Pinguet F, Quantin X. FDA-and EMA-approved tyrosine kinase inhibitors in advanced EGFR-mutated non-small cell lung cancer: Safety, tolerability, plasma concentration monitoring, and management. Biomolecules,2019:9(11):668.
25. Srivastava V, Gupta SP, Siddiqi MI, Mishra BN. Molecular docking studies on quinazoline antifolate derivatives as human thymidylate synthase inhibitors. Bioinformation,2010:4(8):357-61.
26. Vora J, Patel S, Athar M, Sinha S, Chhabria MT, Jha PC, Shrivastava N. Pharmacophore modeling, molecular docking and molecular dynamics simulation for screening and identifying anti-dengue

phytocompounds. J Biomol Struct Dyn, 2019, 1-15. doi:10.1080/07391102.2019.1615002.
27. Wallace AC, Laskowski RA, Thornton JM. LIGPLOT: A program to generate schematic diagrams of protein-ligand interactions. Protein Eng Des Sel,1995:8(2):127-34.
28. Wang M, Herbst RS, Boshoff C. Toward personalized treatment approaches for non-small-cell lung cancer. Nat Med,2021:27(8):1345-56.
29. Wolf A, Oeffinger KC, Shih TY-C, Walter LC, Church TR, Fontham ET, *et al*. Screening for lung cancer: 2023 guideline update from the American Cancer Society. CA Cancer J Clin,2023:73(5):348-66.
30. Yang H, Lou C, Sun L, Li J, Cai Y, Wang Z, *et al*. admetSAR 2.0: Web-service for prediction and optimization of chemical ADMET properties. Bioinformatics,2019:35(6):1067-9.