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Computational evaluation of Fenugreek-derived compounds as FGFR2 inhibitors for cancer therapy

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ABSTRACT

Fibroblast Growth Factor Receptor 2 (FGFR2) is an important target in cancer therapy, particularly breast cancer, where its overexpression is associated with disease progression and poor prognosis. Current treatments face limitations such as drug resistance and adverse side effects, underscoring the need for alternative therapeutic agents. This study investigated fenugreek-derived phytochemicals as potential FGFR2 inhibitors using an integrated computational approach encompassing Molecular Docking, Molecular Dynamics (MD) simulations, and Quantitative Structure-Activity Relationship (QSAR) analyses. Molecular docking identified vitexin as the compound with the highest binding affinity (-13.35 kcal/mol). Molecular Mechanics-Generalized Born Surface Area (MM/GBSA) calculations highlighted fenugreekine as having the most favorable binding energy (-78.55 kcal/mol) relative to the reference drug derazantinib (-75.25 kcal/mol). MD simulations further supported these findings, revealing that vitexin possessed the

least atomistic deviation, with a Root Mean Square Deviation (RMSD) of 1.15 Å compared to the standard drug derazantinib, which had a higher RMSD of 1.67 Å, indicating greater conformational stability of vitexin at the binding site of FGFR2. Vitexin and other top-performing compounds exhibited compact structural conformations with low Radius of Gyration (RoG) values (3.81 Å, 3.74 Å, and 4.38 Å, respectively) compared to derazantinib. These findings suggest that fenugreek-derived phytochemicals, particularly fenugreekine and vitexin, are promising candidates for FGFR2-targeted therapies. However, experimental validation through *in vitro* and *in vivo* studies is essential to confirm their therapeutic potential and advance these compounds toward clinical applications.

Keywords: FGFR2 Inhibitors, Breast Cancer, Fenugreek Phytochemicals, Molecular Docking, Molecular Dynamics, QSAR Analysis.

INTRODUCTION

Globally, cancer stands out as a non-infectious disease that kills more people than all HIV/AIDS cases combined (1). One of the main causes of cancer-related illness and death is breast cancer. According to the GLOBOCAN 2018 estimates of cancer incidence and mortality, breast cancer was the second most frequently diagnosed cancer, accounting for over 11.6% of all female malignancies. It also accounted for 6.6% of all cancer deaths globally, making it the sixth most common cause of cancer fatalities. Breast cancer causes a loss of 14.8 million Disability Adjusted Life Years (DALYs), resulting in a significant public health burden (2). The trans membrane receptor tyrosine kinase Fibroblast Growth Factor Receptor 2 (FGFR2) is essential for coordinating cellular processes such as survival, differentiation, and proliferation (3). To maintain tissue balance and cellular functions, FGFR2 signaling must be properly regulated. Dysregulated FGFR2 signaling, caused by genetic changes or aberrant expression, can be attributed to a number of diseases, most notably cancer (4). Since FGFR2 is known to be an oncogene driver, it has become a desirable target for therapeutic research. Precisely reducing FGFR2's aberrant activity may help stop cancer cell growth and survival while protecting healthy cells (5). The search for new FGFR2 inhibitors has attracted significant attention because it has the potential to transform precision medicine by allowing doctors to customize treatment based on each patient's unique genetic abnormalities and signaling characteristics. These new treatments target the underlying biological causes of disease, improving patient outcomes and potentially overcoming current

constraints in cancer treatment (6). Fibroblast Growth Factors (FGFs) are a family of growth factors that coordinate physiological processes such as angiogenesis, tissue repair, and embryogenesis by sending signals through Fibroblast Growth Factor Receptors (FGFRs). Among the FGFR isoforms (FGFR1 to FGFR4), FGFR2 is the most prominent due to its extensive tissue distribution, critical function in developmental processes, and preservation of internal stability (homeostasis) (7). However, abnormal FGFR2 activity caused by overexpression, mutations, or amplifications can trigger hyperactive signaling pathways that contribute to cancer development and oncogenesis. Several forms of cancer have been found to exhibit FGFR2 abnormalities, highlighting the protein's clinical importance as a potential therapeutic target (7). One of the biggest challenges in drug discovery is creating FGFR2 inhibitors that are both selective and efficacious. Selectivity is essential to prevent negative effects since non-specific inhibition of FGFR1 or FGFR3 which share sequence homology with FGFR2 may have adverse consequences (8).

Medicinal plants have been employed by humanity to prevent disease since the beginning of civilization. A World Health Organization evaluation found that more than 75% of people still rely on plant-derived medicines, primarily from traditional healers, to address their basic medical needs (9). Fenugreek (*Trigonella foenum-graecum*) is one of the earliest known medicinal plants cultivated and has been demonstrated in numerous studies to contain antioxidant qualities in both its seeds and leaves (10). The medicinal benefits of fenugreek seeds include antibacterial properties, stomach stimulation, hypocholesterolemic effects, lactation aid, antidiabetic effects, galactagogue properties, hepatoprotection, and anticancer effects. These positive physiological effects are largely attributed to fenugreek's inherent dietary fiber content, which holds promising nutraceutical value (11). A computer-aided molecular modeling technique was used to examine the potential of phytochemicals from fenugreek acting as inhibitors against Fibroblast Growth Factor Receptor 2 (FGFR2). This comprehensive approach employs molecular docking, MM/GBSA calculations, structure-based screening, molecular dynamics (MD) simulation, quantum calculations via Density Functional Theory (DFT), and ADMETox screening to screen a library of phytochemicals from fenugreek.

METHODS:

Retrieval of receptor

The three-dimensional (3D) X-ray crystallographic structure of FGFR2 co-crystallized with the selective inhibitor N-{4-[4-amino-5-(4-methoxyphenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl}prop-2-enamide, resolved at 2.24 Å with accession ID 8SWE, was retrieved from the RCSB Protein Data Bank. Using Maestro, the PDB data was processed, and the protein preparation wizard was employed to prepare the proteins. As part of the preparation, constrained energy minimization, the inclusion of missing side chains, the removal of water and unconventional ligands, and adjustments to hydrogen placement were all required.

Preparation of compounds from fenugreek

Fenugreek has been reported to contain about two hundred and six (206) active compounds, which were gathered from published literature sources (Wani and Kumar, 2018; Arunabha and Bhattacharjee, 2019; Alu'datt et al., 2024). To identify these compounds, we searched PubChem for their chemical names or structures. Following that, the compounds were downloaded in SDF format by selecting the SDF file format from the "Download" option on the PubChem compound information page. Similar methods were used to obtain derazantinib, the standard drug. The LigPrep tool was then used to prepare each compound using the OPLS_2005 force field once they had been imported into the Schrödinger workspace. Furthermore, the FGFR2 co-ligand N-{4-[4-amino-5-(4-methoxyphenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl}prop-2-enamide was also looked up and downloaded in SDF format from PubChem via the same procedure. As a reference, this ligand was prepared in the same way as the standard drug, derazantinib.

Receptor grid generation

The grid generation job was configured, and a receptor structure was specified using the receptor grid panel. The receptor grid shows the region of the receptor where the ligand and protein interact. The created protein grid was placed on the binding site (Glide Grid) using the Receptor Grid Generation tool. The binding domain of the protein FGFR2 was generated by choosing the co-crystallized ligand to define the coordinates. All amino acid residues at the active site were automatically synthesized into a cubic grid box. The three-dimensional coordinates of the generated grid were (x = -29.2 Å, y = 16.87 Å, z = -21.56 Å) for 8SWE, respectively.

Molecular docking

Docking was performed using Maestro 13.4 (Schrödinger 2022) with the Glide tool. Using three hierarchical docking filtering methodologies, derazantinib (the standard drug), the co-crystallized ligand, and two hundred and six (206) compounds from fenugreek were virtually screened. The large number of ligands was quickly screened using High-Throughput Virtual Screening (HTVS) docking precision, which has considerably more limited conformational sampling than existing precision filters. Thus, using HTVS docking, the 206 compounds were screened against FGFR2. The Standard Precision (SP) filtering technology was utilized to conduct additional screening on the top twenty hit compounds. Using the Extra Precision (XP) scoring algorithm, five (5) hits that had docking affinities greater than those of the reference drug (derazantinib) were screened further. The docking protocol was validated through a redocking procedure to ensure the accuracy of the docking parameters.

Generation and utilization of an Auto-QSAR model for predictive analysis

The FASTA sequence of the ribonucleotide reductase experimental inhibitory dataset was obtained from EBI ChEMBL. Bioactive compounds exhibiting inhibitory effects against the target were identified alongside their pIC50 values. DataWarrior (version 2) converted these datasets into SDF format (Omoboyowa, 2022). The SDF file was created using macro-model minimization and subsequently imported into the Maestro-Schrödinger suite workspace. Based on the pIC50 values of the active compounds, a quantitative structure-activity relationship (QSAR) model was created for the compound of interest. The highest-ranking prediction model (kpls_molprint2D_25) was selected, and it was used to predict the pIC50 values of the five hits obtained from the docking study.

Molecular Mechanics/Generalized Born Surface Area

The docked protein-ligand complex binding free energy was calculated by the MM/GBSA continuum solvent model. The Optimized Potentials For Liquid Simulation, Version 3 (OPLS3) force field and the Variable-Dielectric Surface Generalized Born Solvent Model (VSGB) solvent model were combined with rotamer search methods from Prime. The binding free energy was calculated using the following equation:

$$\Delta G_{\text{bind}} = G_{\text{complex}} - (G_{\text{protein}} + G_{\text{ligand}}) \quad (1)$$

Where ΔG_{bind} is the protein-ligand complex's binding free energy, G_{complex} is the complex's free energy, and G_{protein} and G_{ligand} , respectively, are the free energies of the protein and the ligand.

Molecular Dynamic (MD) Simulation

For the study of protein dynamics and the thorough identification of the binding mechanism of receptor-ligand interaction systems, molecular dynamics is an essential computational technique. According to Genheden and Ryde (2015), the protein system's binding free energy (BFE) was determined using the generalized Born surface area/molecular mechanics (MM/GBSA) approach. The Schrödinger suite's Desmond module was used to carry out the MD simulation for FGFR2. In MD simulation tests, the hit compounds vitexin, kaempferol 7-*O*-glucoside, isovitexin, the conventional medication (derazantinib), and the co-crystallized ligand were docked complexes with the Apo (unbound protein). All three distances were fixed at 10 Å, the box size was computed as a buffer, the volume of the box was kept to a minimum, and the protein-ligand complexes were housed in an orthorhombic box. The Transferable Intermolecular Potential 3 Points (TIP3P) water model was utilized as the solvent design. Salt concentration was established at 0.15 M to simulate physiological circumstances, and sodium ions were injected to balance the system's overall charge. A 10 x 10 x 10 Å orthorhombic boundary box was utilized to prepare the system, and the OPLS3e force field was applied while minimizing the box (Omirin et al., 2023). Initially, the system was minimized and prepared using standard Maestro environment methods. System relaxation was performed in an NPT ensemble at 300 K and 1.01325 bar of pressure. The MD simulation was run for 100 nanoseconds (ns) with trajectory sampling set at 100 ps intervals and 1000 frames total in order to thoroughly sample the conformational space (Ejeje et al., 2024). The simulation trajectories were produced using C- α root mean square deviation (RMSD) (Lee et al., 2017), root mean square fluctuation (RMSF) (Dong et al., 2018), radius of gyration (RoG) (Lobanov et al., 2008), trajectory snapshots, and solvent-accessible surface area (SASA) (Roe and Cheatham, 2013), the atomic interactions between the protein and ligand were examined in depth using these MD parameters (Adewumi et al., 2024). An MS-MD trajectory analysis and a simulation interaction diagram were used to illustrate and interpret the simulation's outcomes. Origin version 6.0 was used to visualize the data.

ADME/Tox screening

The pharmacokinetic profile, drug-likeness, and toxicity of the hit compounds were evaluated along with their absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties using the AdmetSar web server, Pro-Tox II web server, and the QikProp module within Schrödinger's Maestro interface.

Density Functional Theory (DFT)

Quantum chemical analyses and density functional theory (DFT) were utilized to evaluate the molecular characteristics of fenugreek compounds to forecast the biological activities of the top-ranked compounds. The most stable conformer was chosen following a conformer distribution calculation using the computational chemistry program Spartan 10 to perform DFT analysis in a vacuum. EHOMO and ELUMO, two thermodynamic parameters, were computed from this analysis. The global reactivity descriptors and other features were then derived using these values. For instance, the difference between ELUMO and EHOMO was used to calculate the energy band gap.

$$E_g = E_{LUMO} - E_{HOMO} \quad (1)$$

Koopman's theory connects the Ionization energy (I) and Electron Affinity (A) to EHOMO and ELUMO (Koopmans, 1993).

$$I = -E_{HOMO} \quad (2)$$

$$A = -E_{LUMO} \quad (3)$$

$$\chi = \frac{I+A}{2} \quad (4)$$

$$\eta = \frac{I-A}{2} \quad (5)$$

$$\delta = \frac{1}{\eta} \quad (6)$$

RESULTS/DISCUSSION:

Docking/MMGBSA:

The docking scores and MM/GBSA screening outcomes for the hit compounds are represented graphically in Fig 1 and Table 1, respectively. To assess the potential inhibitory effects of the chosen fenugreek ligands, the target protein's FGFR2 binding pocket was docked with enhanced precision (XP). In addition to examining the structural interactions of the top compounds, important amino acid interactions at the FGFR2 binding site were identified.

Table 1: The binding affinity (kcal/mol) and MMGBSA of the top-ranked *fenugreek* phytochemical constituents and standard drug against the FGFR2 target.

s/n	Compound name	PubChem Cid	Docking score(kcal/mol)	MMGBSA (ΔG bind)
1	vitexin	5280441	-13.35	-57.46
2	fenugreekine	444170	-13.258	-78.55
3	Quercetin	5280343	-12.339	-50.71
4	Kaempferol 7-O- glucoside	10095180	-12.168	-61.05
5	isovitexin	162350	- 11.932	- 44.2
6	Derazantinib(standard)	46834118	-11.208	-75.25
7	Co-crystallized Ligand	170459232	-10.888	-56.5

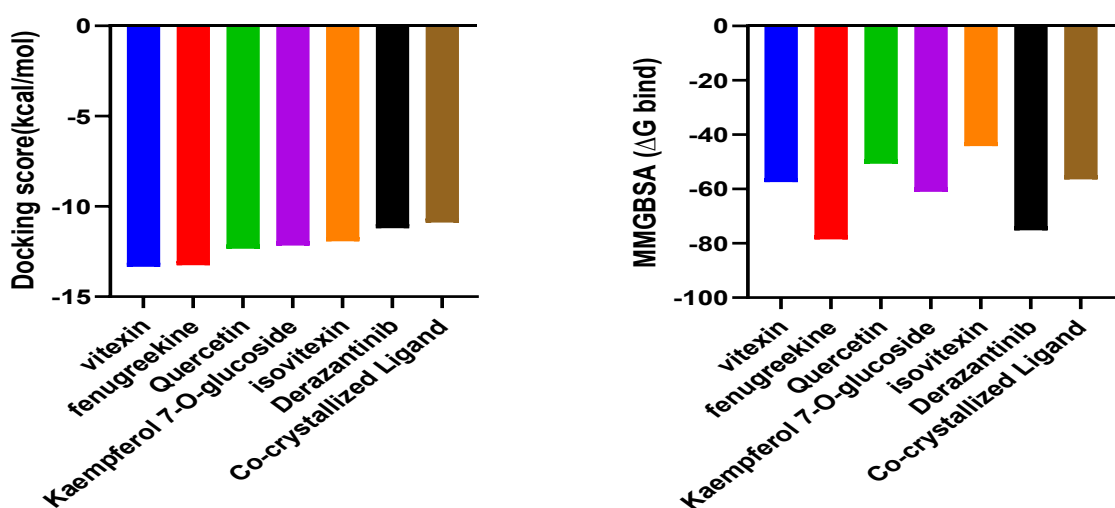
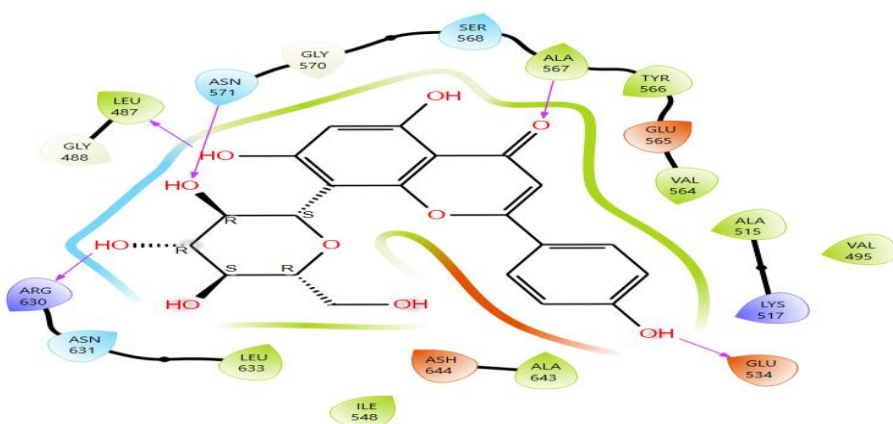


Fig.1: Graphical Representation of the Binding Free Energy (Docking Score) and Prime/MM-GBSA (ΔG_{bind}) Binding Energy for Docking Complexes.

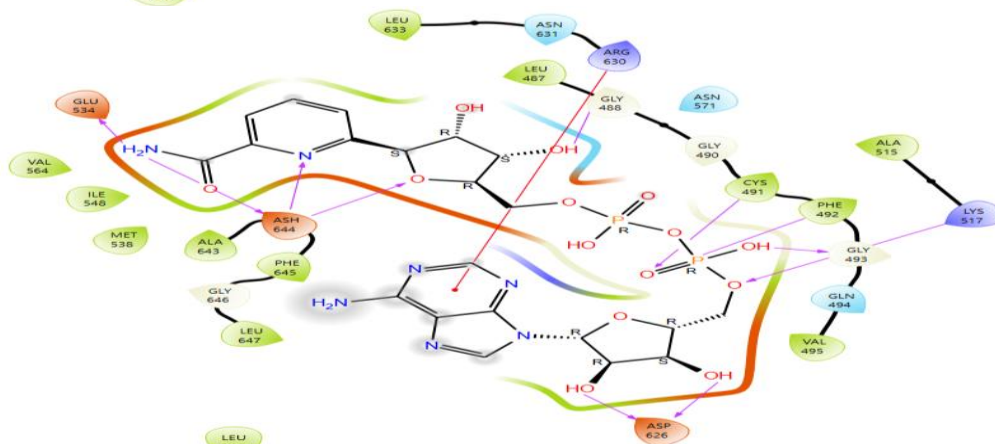
The docking and MM/GBSA results for the top five ligands provide valuable insights into their binding potential and stability with the FGFR2 protein. The docking scores presented in Table 1 and Figure 1 indicate that vitexin had the highest affinity, with a docking score of -13.35 kcal/mol, followed by fenugreekine (-13.258 kcal/mol), quercetin (-12.339 kcal/mol), kaempferol 7-O-glucoside (-12.168 kcal/mol), and isovitexin (-11.932 kcal/mol). Notably, these ligands demonstrated superior binding affinity compared to the reference drug derazantinib (-11.208 kcal/mol) and the co-crystallized ligand (-10.888 kcal/mol). To validate these findings, MM/GBSA calculations were performed to estimate the binding free energies of the docked protein-ligand complexes. The MM/GBSA results revealed that fenugreekine exhibited the most favorable binding energy of -78.55 kcal/mol, outperforming both derazantinib (-75.25 kcal/mol) and the co-crystallized ligand (-56.5 kcal/mol). This discrepancy between docking scores and MM/GBSA binding free energies can be attributed to the fundamental differences between these methods. Docking scores provide a preliminary estimate of binding affinity based on simplified scoring functions that do not fully account for solvent effects or conformational flexibility. In contrast, MM/GBSA offers a more rigorous assessment by incorporating solvation energy and detailed molecular interactions, leading to a more accurate evaluation of ligand stability within the binding site (28),(29). The difference in ranking observed between docking and MM/GBSA

analyses suggests that fenugreekine forms more stable and energetically favorable interactions with FGFR2 when solvent effects and molecular flexibility are considered. The reliability of MM/GBSA in identifying stable binding sites has been demonstrated in previous studies. Combining docking and MM/GBSA analyses allows for a more comprehensive evaluation of ligand-binding potential, with MM/GBSA serving as a dependable method for assessing the structural stability and interaction strength of protein-ligand complexes. Hence, while vitexin demonstrated the highest docking score, the MM/GBSA results identified fenugreekine as the ligand with the most favorable binding energy. Furthermore, we investigated the structural relationships between the leading compounds, the standard compound, and the co-crystallized ligand, as well as the crucial amino acid interactions in the FGFR2 binding region. Table 2 and Fig. 2 show that vitexin formed five hydrogen bonds with GLU534, ARG630, LEU487, ASN571, and ALA567 without pi-pi stacking. Fenugreekine produced eight hydrogen bonds with ARG630, GLY493, LYS517, PHE492, CYS491, ASP626, ASH644, and GLU534, along with pi-pi stacking involving ARG630. Quercetin interacted with LEU487, ALA567, GLU565, GLU534, and ASH644 without pi-pi stacking. Kaempferol 7-O-glucoside formed four hydrogen bonds with ARG630, ASN571, GLU534, and GLU565 without pi-pi stacking. Isovitexin formed four hydrogen bonds with ALA515, GLU534, ASH644, and SER568 without pi-pi stacking. Derazantinib formed one hydrogen bond with ALA567 and exhibited pi-pi stacking with LYS517. Additionally, the co-crystallized ligand formed two hydrogen bonds with GLU565 and ALA567 without pi-pi stacking. In the vast network of interactions involving fenugreekine, the contact with CYS491, a residue essential for covalent inhibition (30), is particularly important. Due to its interaction with CYS491, fenugreekine is positioned as a prospective candidate for FGFR2 inhibition, potentially outperforming the standard drug

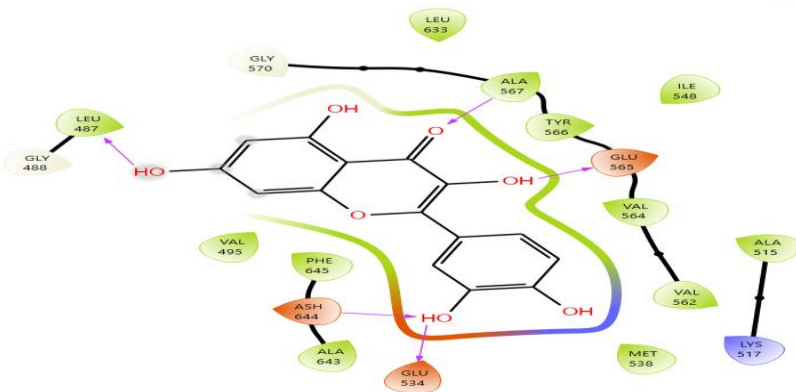
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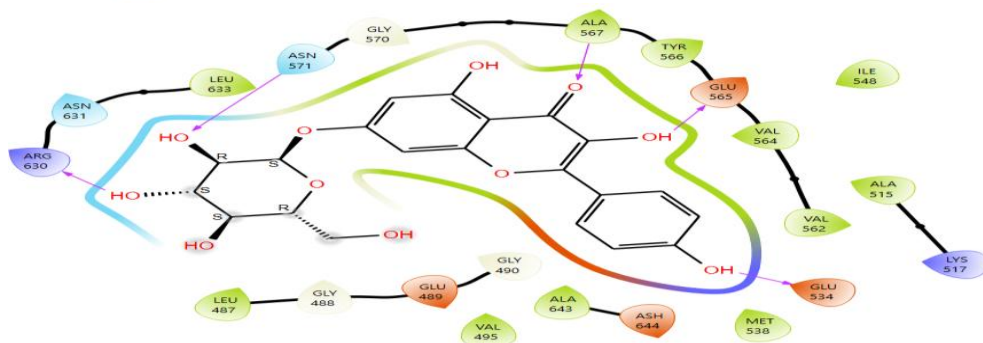
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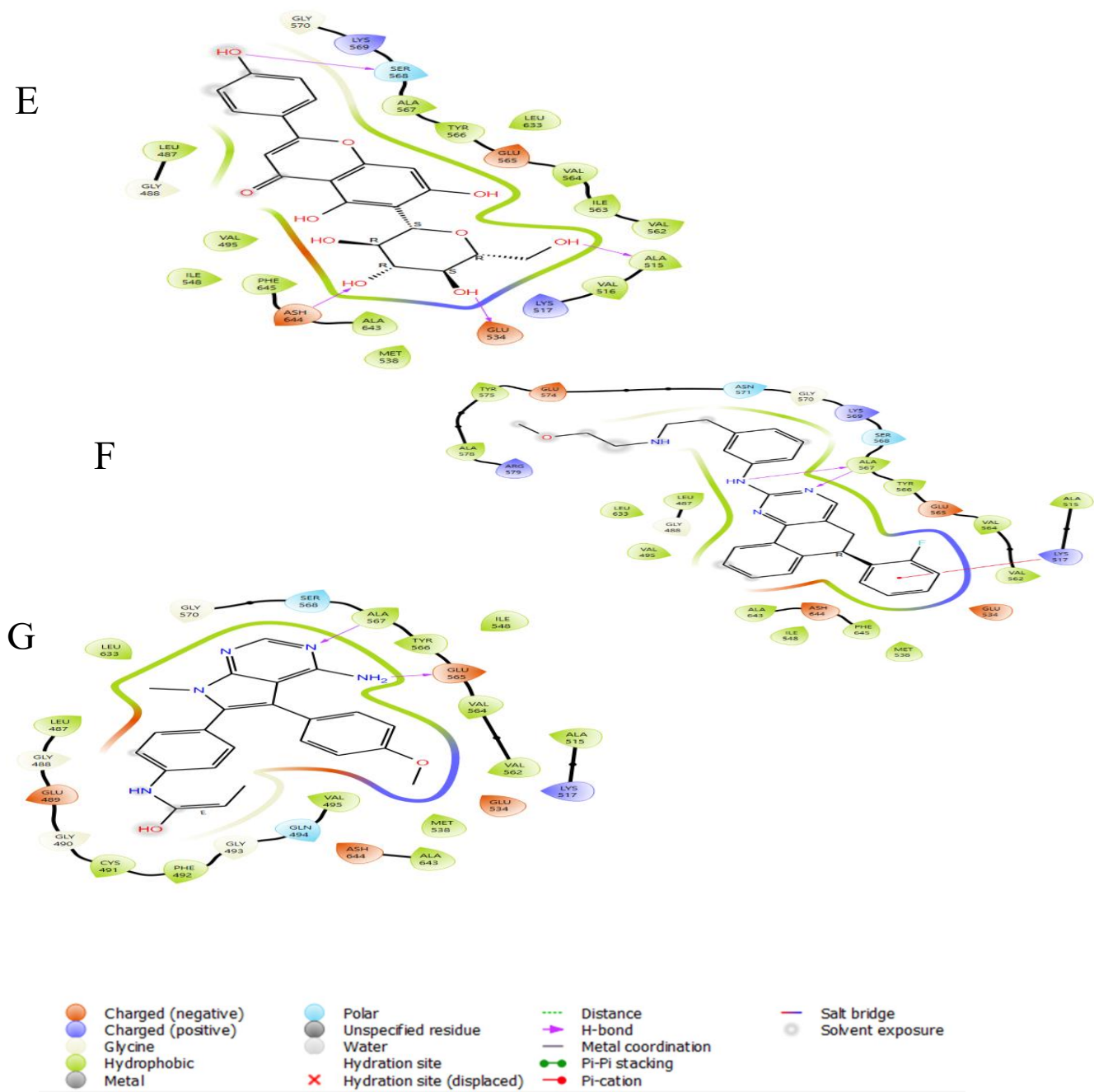


C



D





2D Molecular Interaction of Hit Compounds (Fenugreek) with the Binding Pocket of FGFR2 (A) Vitexin (B) Fenugreekine (C) Quercetin (D) Kaempferol 7-O-glucoside (E) Isovitexin (F) Standard (G) Co-crystallized Ligand.

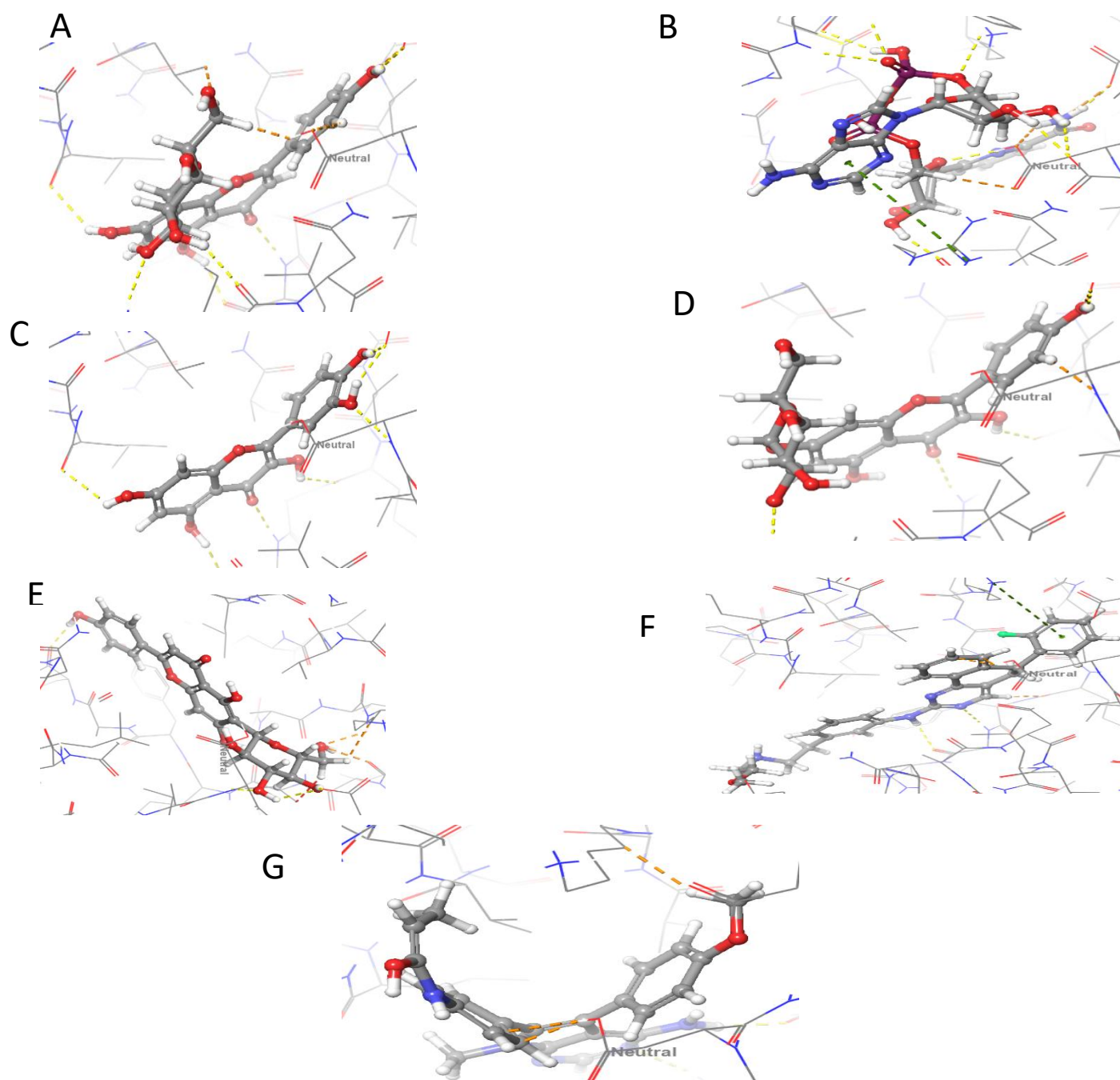


Fig. 3: 3D Molecular Interaction of Hit Compounds (Fenugreek) with the Binding Pocket of FGFR2 (A) Vitexin (B) Fenugreekine (C) Quercetin (D) Kaempferol 7-O-glucoside (E) Isovitexin (F) Standard (G) Co-crystallized Ligand.

TABLE 2: Molecular contact profiling of the top *Fenugreek* phytochemicals and standard drug.

COMPOUND NAME	H-BOND INTERACTION	HYDROPHOBIC AMINO ACID	OTHER INTERACTION
Vitexin	GLU534, ARG630, LEU487, ASN571, ALA567	VAL495, PHE645, ALA643, LEU633, ALA515, VAL564, TYR566, ALA567, LEU487	NONE
Fenugreekine	ARG630, GLY493, LYS517, PHE492, CYS491, ASP626, ASH644, GLU534	LEU633, ALA515, VAL495, PHE492, LEU487, CYS491, LEU647, PHE645, ALA643, ILE548, MET538, VAL564	PI-PI-STARKING: ARG630
Quercetin	LEU487, ALA567, GLU565, GLU534, ASH644	ALA515, VAL495, PHE645, MET538, VAL562, ALA643, VAL564, TYR566, ILE548, ALA567, LEU633, LEU487	NONE
Kaempferol glucoside	7-O- ARG630, ASN571, GLU534, GLU565	MET538, VAL562, VAL564, TYR566, ALA567, LEU633, LEU487, VAL495, VAL562, ALA643, ALA515, ILE548	NONE
Isovitexin	ALA515, GLU534, ASH644, SER568	MET538, ALA515, VAL516, VAL495, LEU487, ALA567, LEU633, VAL564,	NONE

		ILE563, VAL562,	
		ILE548, PHE645,	
		ALA643, MET538	
Derazantinib(standard)	ALA567,	ALA643, VAL495,	PI-PI-STARKING:
		LEU487, ALA578,	LYS517
		TYR575, LEU633,	
		ALA567, TYR566,	
		ALA515, VAL564,	
		VAL562, MET538,	
		PHE645, ALA643,	
		ILE548	
Co-crystallized	GLU565,ALA567	MET538, VAL562,	NONE
Ligand.		VAL564, ALA515,	
		TYR566, ILE548,	
		ALA567, LEU633,	
		LEU487, VAL495,	
		ALA643, PHE492,	
		CYS491	

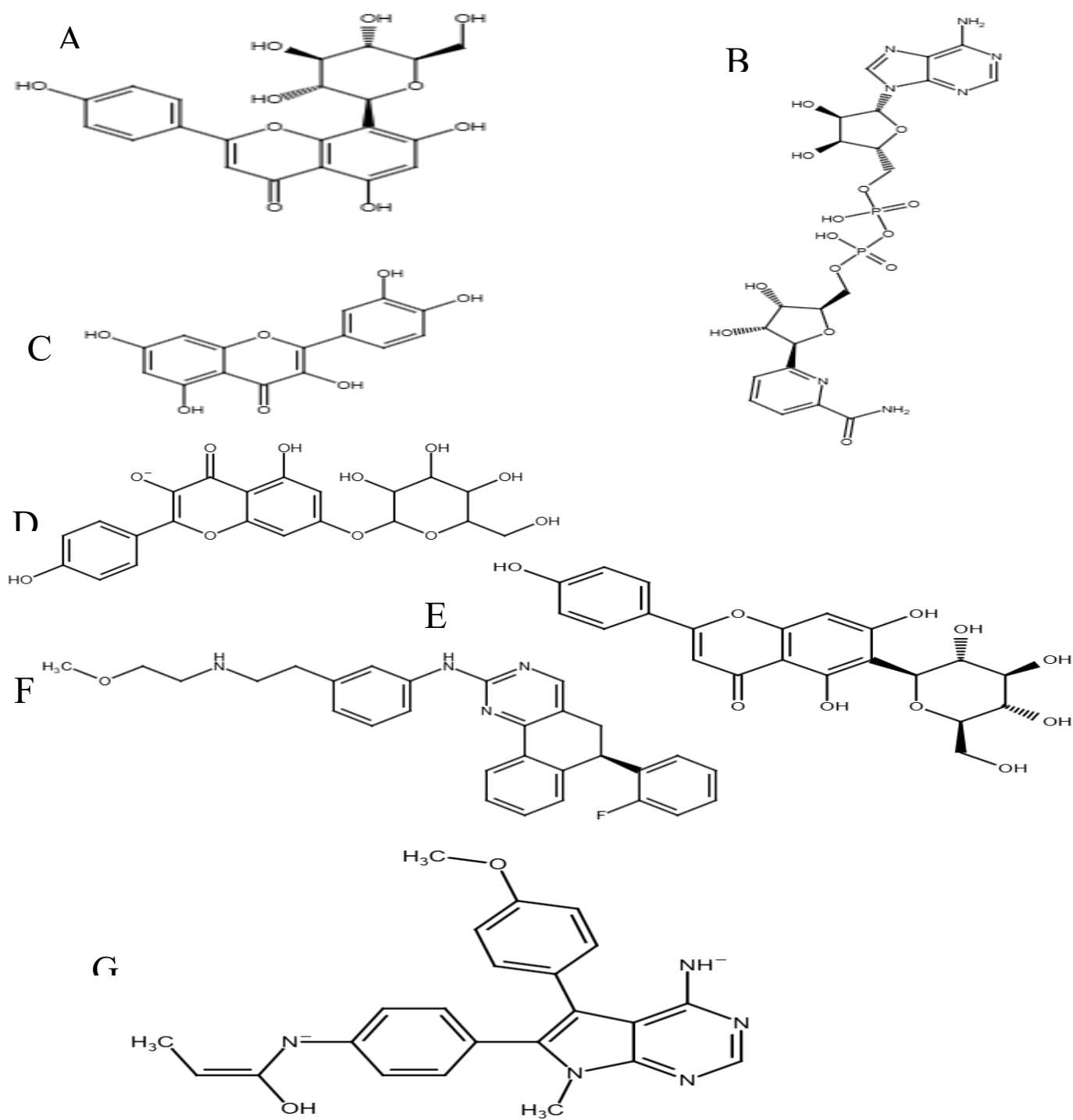


Fig. 4: Molecular Structure of hit compounds (*Fenugreek*) (A) Vitexin (B) Fenugreekine (C) Quercetin (D) Kaempferol 7-O-glucoside (E) Isovitexin (F) Standard drug (G) Co-crystallized Ligand.

Auto QSAR analysis:

A computer method that illustrates the association between tiny compounds' structural characteristics and biological functions is called the quantitative structure-activity relationship, or QSAR. In drug development, this model is crucial (31). Several topological descriptors are used by AutoQSAR, a Schrödinger suite program, to construct autonomous variable simulations (28). As indicated in Table 4, the partial least squares regression (kpls) analysis (kpls_molprint2D_25) was chosen as the best model among the predictive models produced in the QSAR study. It had a test set of 24.3% and a train set of 75.7% (Test Set: 9; Train Set: 28). According to Table 4, the predictive model indices showed a Q² value of 0.357, a root mean square error (RMSE) of 0.9161, a standard deviation (SD) of 0.3547, and an R² value of 0.8986. The model displayed fewer points in the test set (red) than in the training set (blue), indicating a significant association with Table 5. Fig.6 displays the scatter plot of the predicted activity against the observed activity. The pIC₅₀ values for the hit compounds in Table 3 were obtained using the QSAR model. All of the hit compounds, co-crystallized ligand, and the standard medication exhibited high pIC₅₀ over 7.00 μ M, with Kaempferol 7-O-glucoside (7.907 μ M) having the best pIC₅₀ when compared to the co-ligand (7.569 μ M) and Derazantinib (standard drug = 7.251 μ M).

Table 3: Hit compounds Predicted pIC₅₀ using QSAR model.

s/n	Compound name	PubChem Cid	Pred Y
1	vitexin	5280441	7.842
2	fenugreekine	444170	7.668
3	Quercetin	5280343	7.744
4	Kaempferol 7-O-glucoside	10095180	7.907
5	isovitexin	162350	7.842
6	Derazantinib(standard)	46834118	7.251
7	Co-crystallized Ligand	170459232	7.569

Table 4: Corresponding parameters to the predicted model generated.

Training	Set	Test	Set
S.D.	R ²	RMSE	Q ²
0.3547	0.8986	0.357	0.9161

Table 5: Predicted activities vs observed activities of the Auto-QSAR.

ID	Set	Y(Obs)	Y(Pred)	Error	Name
1	test	8.37	7.9963	-0.3737	Compound
2	train	8.15	8.7202	0.5702	Compound
3	train	9	8.9371	-0.0629	Compound
4	train	6.36	6.4199	0.0599	Compound
5	train	7.69	7.4388	-0.2512	Compound
6	train	6.49	6.1715	-0.3185	Compound
7	train	8.47	8.8199	0.3499	Compound
8	train	5.34	6.1076	0.7676	Compound
9	test	5.16	5.1213	-0.0387	Compound
10	train	5.2	5.9513	0.7513	Compound
11	test	7.43	8.0096	0.5796	Compound
12	train	7.26	7.5091	0.2491	Compound
13	train	6.84	6.946	0.106	Compound
14	train	8.06	8.32	0.26	Compound
15	train	7.89	7.8329	-0.0571	Compound
16	test	8.09	7.7529	-0.3371	Compound
17	train	7.95	7.7292	-0.2208	Compound
18	train	8.09	7.814	-0.276	Compound
19	test	8.54	7.8504	-0.6896	Compound
20	train	8.05	8.1978	0.1478	Compound
21	train	8.54	8.591	0.051	Compound
22	train	8.73	8.4947	-0.2353	Compound
23	train	7.58	7.3163	-0.2637	Compound
24	test	6.11	6.2376	0.1276	Compound
25	train	6.46	6.344	-0.116	Compound
26	train	7.2	6.4167	-0.7833	Compound

27	test	4.62	5.1059	0.4859	Compound
28	train	4.92	4.8254	-0.0946	Compound
29	train	5.39	5.1714	-0.2186	Compound
30	train	6.11	6.6137	0.5037	Compound
31	test	6.61	6.5685	-0.0415	Compound
32	train	7.16	6.9313	-0.2287	Compound
33	train	8.18	8.1783	-0.0017	Compound
34	test	6.66	6.8178	0.1578	Compound
35	train	6.77	6.4006	-0.3694	Compound
36	train	7.04	7.8211	0.7811	Compound
37	train	7.43	7.5316	0.1016	Compound
38	train	7.66	7.213	-0.447	Compound
39	train	6.27	6.5914	0.3214	Compound
40	train	8.75	8.8199	0.0699	Compound
41	train	7.82	7.7246	-0.0954	Compound
42	train	8.92	9.024	0.104	Compound
43	train	7.82	8.1326	0.3126	Compound
44	train	8.74	8.3126	-0.4274	Compound
45	test	8.62	8.2728	-0.3472	Compound
46	train	8.31	8.5189	0.2089	Compound
47	test	8.69	8.2645	-0.4255	Compound
48	train	8.36	8.002	-0.358	Compound
49	train	8.46	8.4164	-0.0436	Compound
50	train	8.5	8.1656	-0.3344	Compound
51	test	7.83	8.2641	0.4341	Compound
52	train	8.55	8.378	-0.172	Compound
53	train	8.47	8.4148	-0.0552	Compound
54	test	8.29	8.3655	0.0755	Compound
55	train	8.54	8.0609	-0.4791	Compound
56	train	8.46	8.3379	-0.1221	Compound
57	test	7.97	7.7694	-0.2006	Compound

58	train	8.47	8.378	-0.092	Compound
59	train	6.35	6.758	0.408	Compound
60	test	7.6	7.7747	0.1747	Compound

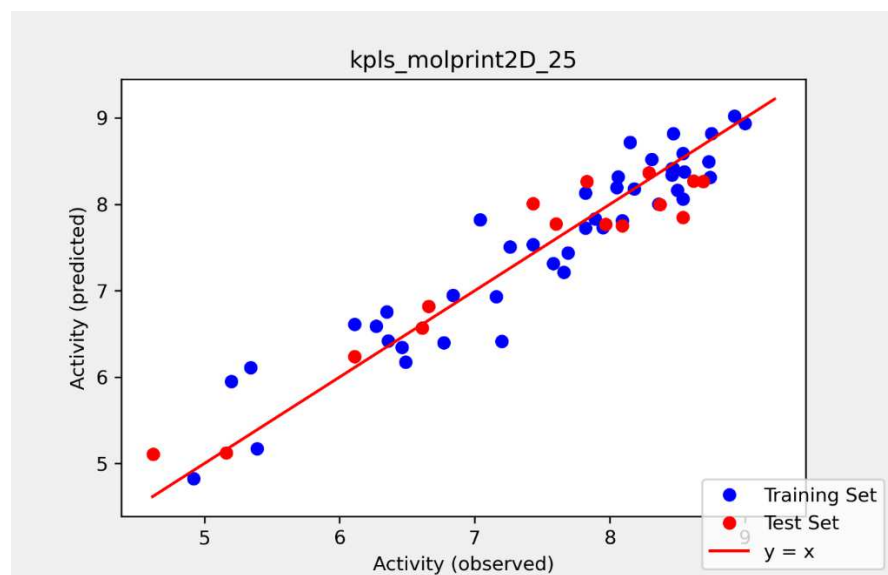
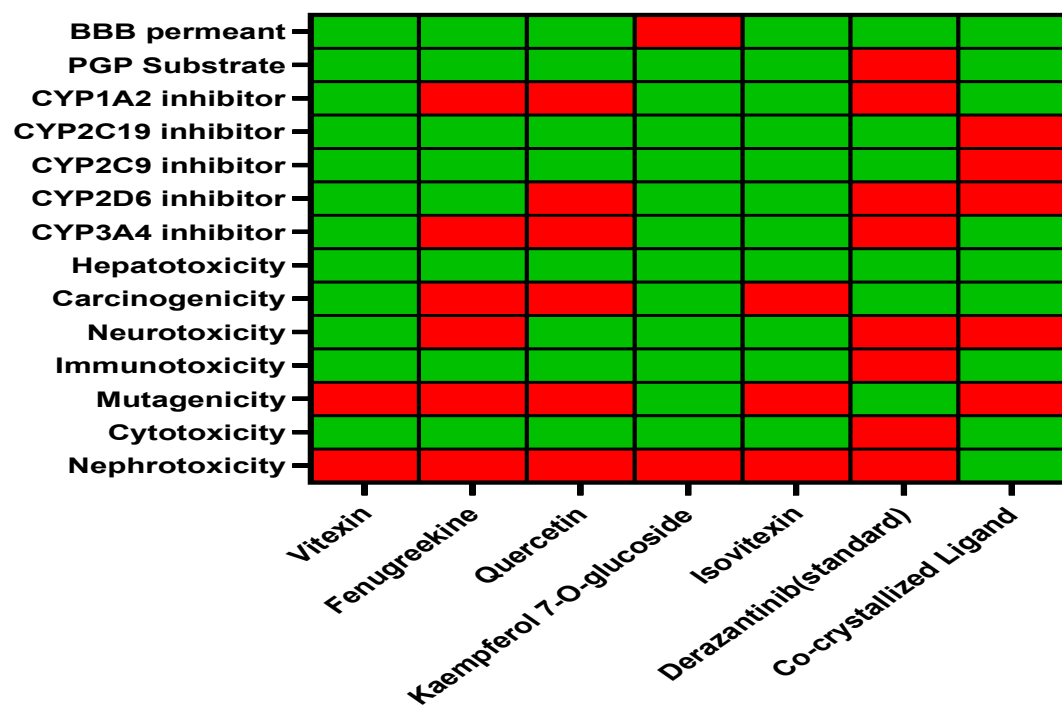


Fig. 6: QSAR Scatter plot of the predicted model.

Table 6: In-silico drug-likeness, oral bioavailability, pharmacokinetic properties, toxicity profile, and cytochrome P450 metabolizing enzyme inhibitory potentials of selected fenugreek phytochemical constituents, co-crystallized ligand, and standard drug.

Compound name	Vitexin	Fenugreekine	Quercetin	Kaempferol, 7-O-glucoside	Isovitexin	Derazantinib (standard)	Co-crystallized Ligand
MW g/mol	432.38	663.43	286.24	448.38	432.38	468.57	399.45
BBB permeant	NO	NO	NO	YES	NO	NO	NO
GI absorption	LOW	LOW	HIGH	LOW	LOW	HIGH	HIGH
PGP Substrate	NO	NO	NO	NO	NO	YES	NO
CYP1A2 inhibitor	NO	NO	YES	NO	NO	YES	NO

CYP2C19 inhibitor	NO	NO	NO	NO	NO	NO	YES
CYP2C9 inhibitor	NO	NO	NO	NO	NO	NO	YES
CYP2D6 inhibitor	NO	NO	YES	NO	NO	YES	YES
CYP3A4 inhibitor	NO	NO	YES	NO	NO	YES	NO
Bioavailability Score	0.55	0.11	0.55	0.17	0.55	0.55	0.85
Hepatotoxicity	NO	NO	NO	NO	NO	NO	NO
Neurotoxicity	NO	YES	NO	NO	NO	YES	YES
Nephrotoxicity	YES	YES	YES	YES	YES	NO	NO
Carcinogenicity	NO	NO	YES	NO	YES	NO	NO
Immunotoxicity	NO	NO	NO	NO	NO	YES	NO
Mutagenicity	YES	NO	YES	NO	YES	NO	YES
Cytotoxicity	NO	NO	NO	NO	NO	YES	NO
LD50:mg/kg	832	7000	159	5000	159	300	1000
Toxicity class	4	6	3	5	3	3	4
Rule of five (5)	1	3	0	2	1	1	0



NO

YES

Fig. 7: The Heat Map of the ADMET Parameters of Selected Fenugreek Phytochemical Constituents, Co-crystallized Ligand, and Standard Drug.

Pharmacokinetic screening:

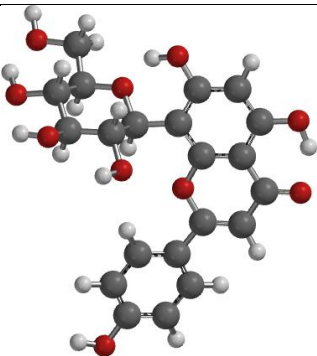
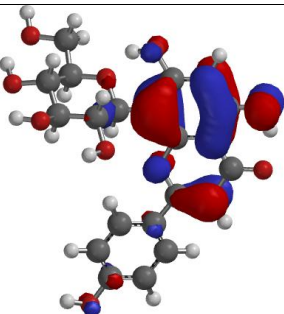
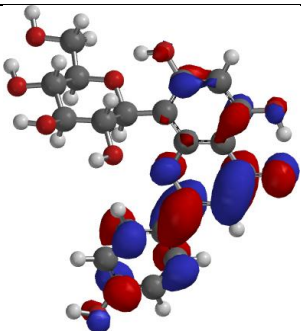
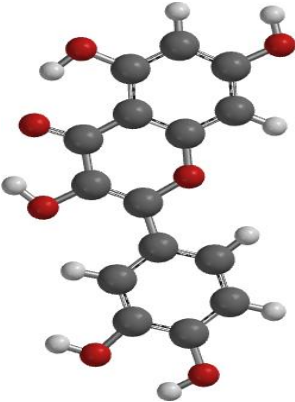
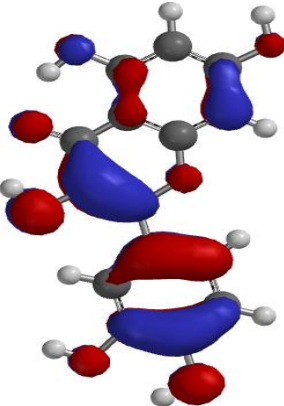
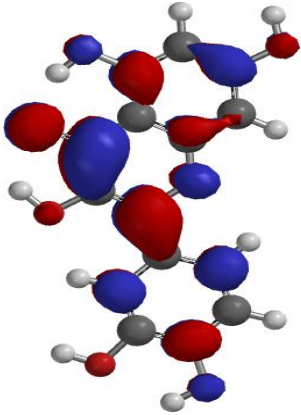
Pharmacokinetic screening is a pivotal step in drug discovery, providing essential insights into how therapeutic candidates interact with biological systems. This study employed *in silico* predictive models to evaluate key pharmacokinetic properties, including blood-brain barrier (BBB) permeability, cytochrome P450 (CYP) enzyme inhibition, P-glycoprotein (P-gp) substrate activity, and oral bioavailability, alongside toxicity profiles. These predictions offer a cost-effective and time-saving approach to prioritize compounds for experimental validation. The ability to permeate the BBB is critical for drugs targeting the central nervous system (CNS), as it determines their bioavailability to the brain while preventing the entry of harmful substances. In this predictive analysis, isovitexin was the only compound capable of crossing the BBB, highlighting its potential for CNS applications. Other compounds, however, were predicted to lack BBB permeability, restricting their utility to peripheral targets. While computational methods for

assessing BBB permeability are not without limitations, they provide a valuable preliminary tool in identifying CNS-compatible compounds. Drug-drug interactions (DDIs), often mediated by the inhibition of cytochrome P450 (CYP) enzymes, can significantly affect the metabolism of co-administered medications. CYP isoforms such as CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 play pivotal roles in the metabolic pathways of numerous pharmaceuticals. The predictions revealed that vitexin exhibited no inhibitory activity against these CYP isoforms, suggesting a low potential for DDIs. Conversely, quercetin, derazantinib, and the co-crystallized ligand inhibited multiple CYP enzymes, including CYP1A2, CYP2D6, and CYP3A4, raising concerns about potential metabolic interactions. Notably, the co-crystallized ligand uniquely inhibited CYP2C19 and CYP2C9, indicating a higher risk for DDIs and necessitating further investigation. The interaction of drugs with P-glycoprotein (P-gp) can influence their bioavailability and clearance. P-gp substrates are actively excreted via bile and urine, which can lead to reduced bioavailability and increased drug clearance (32). The predictive models used in this study indicated that most compounds were not P-gp substrates, with derazantinib being the sole exception. This finding suggests that derazantinib may exhibit reduced bioavailability and higher clearance rates compared to other compounds.

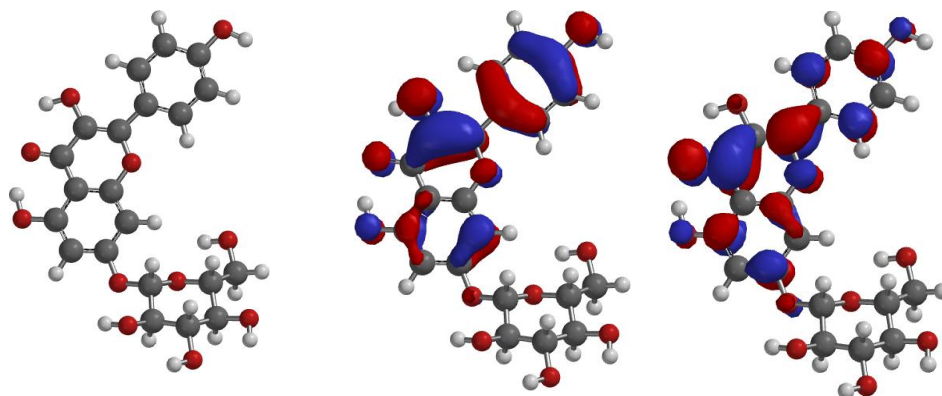
Oral bioavailability a key determinant of a drug's pharmacokinetic profile—was also assessed. Bioavailability scores above 0.5 indicate high oral absorption, while scores below this threshold suggest limited bioavailability (33). The co-crystallized ligand demonstrated the highest bioavailability score (0.85), suggesting superior pharmacokinetic properties. Quercetin, isovitexin, and derazantinib exhibited moderate scores of 0.55, indicating reasonable potential for oral administration. In contrast, fenugreekine scored 0.11, reflecting poor bioavailability and limited suitability for oral delivery. Toxicological predictions were performed to assess the safety profiles of the compounds. None of the compounds were predicted to exhibit hepatotoxicity, indicating a low risk of liver toxicity. However, fenugreekine and derazantinib showed neurotoxicity, raising potential concerns for CNS safety. Nephrotoxicity was identified in vitexin, fenugreekine, quercetin, kaempferol 7-O-glucoside, and isovitexin, suggesting possible kidney damage. Quercetin and isovitexin were predicted to have carcinogenic properties while other compounds including derazantinib appeared inert in terms of cytotoxicity and carcinogenicity. Immunotoxicity was not observed in most compounds; however, derazantinib was an exception that showed potential adverse effects on the immune system. Additionally, vitexin, quercetin, and the co-

crystallized ligand demonstrated mutagenic properties, indicating a risk of genetic mutations. This study highlights the pharmacokinetic potential and safety profiles of several candidate compounds. Isovitexin emerged as a promising CNS drug candidate due to its BBB permeability and moderate bioavailability; however, its nephrotoxicity and carcinogenicity warrant further scrutiny. The co-crystallized ligand displayed the most favorable bioavailability profile but posed risks related to CYP inhibition and mutagenicity. These findings underscore the importance of experimental validation to confirm pharmacokinetic and toxicological predictions and support the development of these compounds into clinically viable drugs.

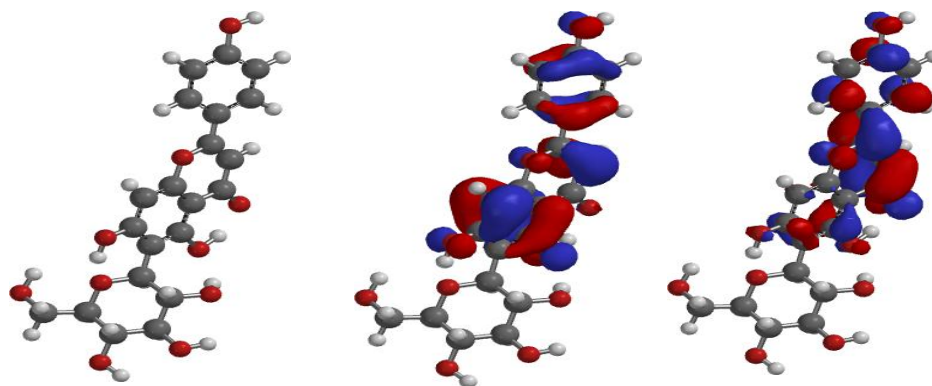
TABLE 7: STRUCTURES OF THE LIGANDS IN OPTIMIZED, HOMO AND LUMO FORM.

Compound	Optimized Structure	HOMO	LUMO
Vitexin			
Quercetin			

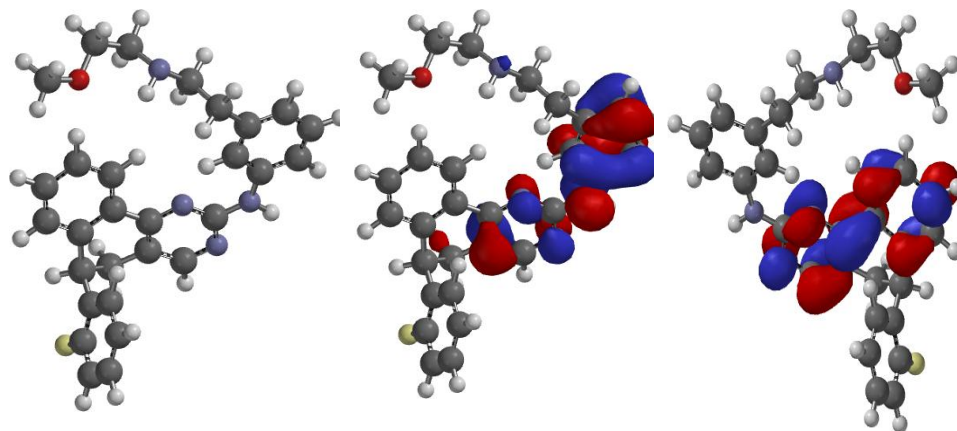
Kaempferol 7-O-glucoside



Isovitexin



Derazantinib



Co-crystallized
Ligand.

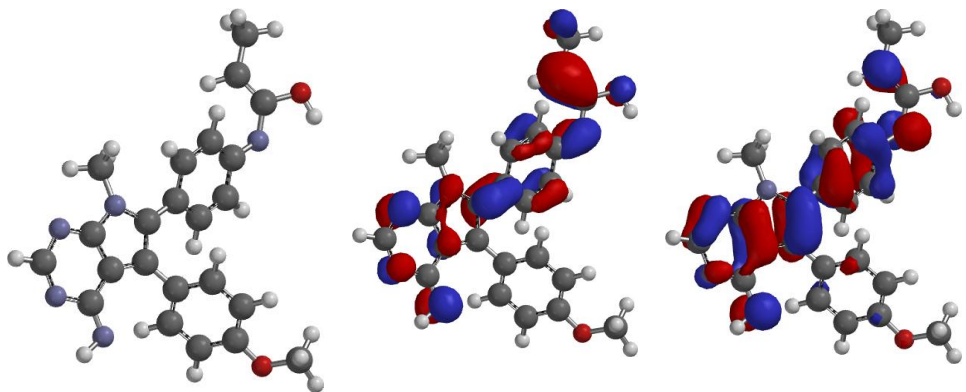


TABLE 8: THE CALCULATED THERMODYNAMIC QUANTITIES (ENTHALPY AND FREE ENERGY) VIA DFT

COMPOUND	E_{HOMO} (eV)	E_{LUMO} (eV)	E_g (eV)	I (eV)	A (eV)	η (eV)	δ (eV ⁻¹)	χ (eV)	ω (eV)
Vitexin	-5.72	-1.52	4.2	5.72	1,52	2.1	0.47619	3.62	3.120095
Quercetin	-5.48	-1.84	3.64	5.48	1.84	1.82	0.549451	3.66	3.68011
Kaempferol 7-O-glucoside	-5.62	-1.91	3.71	5.62	1.91	1.855	0.539084	3.765	3.820815
Isovitexin	-6.15	-1.96	4.19	6.15	1.96	2.095	0.477327	4.055	3.92435
standard drug	-5.29	-1.44	3.85	5.29	1.44	1.925	0.519481	3.365	2.941097
Co-crystallized Ligand.	-5.10	-3.55	1.55	5.1	3.55	0.775	1.290323	4.325	12.06815

Density Functional Theory:

Frontier Molecular Orbitals (FMOs)

The energies of the Frontier Molecular Orbitals (FMOs), specifically the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO), offer critical insights into the reactivity, stability, and electronic properties of potential drug candidates. The HOMO energy reflects a molecule's ability to donate electrons, while the LUMO energy indicates its capacity to accept electrons. The interplay between these orbitals is essential for understanding the optical, electrical, and chemical characteristics of molecules (34). In the context of drug discovery, particularly for FGFR2 inhibitors, the electron-donating and accepting potential of ligands can influence their interaction with the target protein. Among the analyzed compounds, vitexin exhibited the highest HOMO energy ($E_{\text{HOMO}} = -5.72 \text{ eV}$), indicating a significant propensity to donate electrons. Conversely, isovitexin had the lowest HOMO energy ($E_{\text{HOMO}} = -6.15 \text{ eV}$), suggesting it is less likely to donate electrons. The co-crystallized ligand displayed the lowest LUMO energy ($E_{\text{LUMO}} = -3.55 \text{ eV}$), highlighting its strong electron-accepting potential, whereas vitexin had the highest LUMO energy ($E_{\text{LUMO}} = -1.52 \text{ eV}$), indicating reduced electron-accepting capability. The band gap energy, defined as the difference between the E_{HOMO} and E_{LUMO} energies, is a key determinant of a molecule's thermochemical reactivity and stability. A larger band gap correlates with greater stability and lower reactivity, while a smaller band gap suggests higher reactivity and reduced stability. In this study, vitexin and isovitexin exhibited relatively large band gaps of 4.2 eV and 4.19 eV, respectively, indicating their higher chemical stability. In contrast, the co-crystallized ligand had the smallest band gap of 1.55 eV, reflecting greater reactivity and lower stability. Density Functional Theory (DFT) analysis further supports these conclusions by providing comprehensive assessments of global reactivity descriptors (GRDs) such as chemical hardness, softness, electronegativity, and chemical potential. Chemical hardness (η) represents a molecule's resistance to electronic deformation; molecules with higher hardness values are less polarizable and possess wider band gaps. Both vitexin and isovitexin demonstrated the highest hardness values of 2.1 eV and 2.095 eV, respectively, indicating their resistance to electron cloud deformation. Electronegativity (χ) measures a molecule's ability to attract electrons. Kaempferol 7-O-glucoside exhibited the highest electronegativity (3.765 eV), suggesting strong electron-attracting potential, whereas the standard drug, derazantinib, had the

lowest electronegativity (3.365 eV), indicating weaker electron-attracting capability. These findings, combined with the calculated LUMO energies ranging from -1.44 eV to -3.55 eV, underscore the electron-accepting potential of the identified compounds. DFT-derived thermodynamic parameters, including enthalpy and free energy (shown in Table 8 as well as in Table 7), provide additional insights into the stability and feasibility of ligand binding. By integrating docking, MMGBSA, and DFT analyses, this study employs a robust computational drug discovery strategy to identify potential FGFR2 inhibitors. The DFT calculations validate and complement the docking and MMGBSA results, offering a deeper understanding of molecular reactivity, stability, and potential for effective protein-ligand interactions (34).

Molecular Dynamic (MD) Simulation:

Table 9: Interactive properties of MDs of the FGFR2 receptors and protein-ligand interactions.

Complex	RMSD Å (mean ± SEM)	RMSF Å (mean ± SEM)
Vitexin	1.15±0.01	1.00±0.05
fenugreekine	1.55±0.01	0.96±0.05
Quercetin	1.72±0.01	1.06±0.10
Kaempferol 7-O-glucoside	1.69±0.01	0.91±0.05
isovitexin	1.80±0.02	1.01±0.07
Derazantinib	1.67±0.01	0.86±0.05
Co-crystallized Ligand	1.67±0.01	0.96±0.07
APO FGFR2	1.36±0.01	1.01±0.08

Table 10: Interactive properties of MDs of the FGFR2 receptors and protein-ligand interactions.

Complex	RoG Å (mean ± SEM)	SASA Å ² (mean ± SEM)
Vitexin	3.81 ± 0.00	32.78 ± 0.71
fenugreekine	5.33 ± 0.01	194.46 ± 2.09
Quercetin	3.74 ± 0.00	30.00 ± 0.77
Kaempferol 7-O-glucoside	4.38 ± 0.00	58.73 ± 1.03
Isovitexin	4.87 ± 0.00	167.33 ± 1.97
Derazantinib	6.16 ± 0.02	235.00 ± 3.22
Co-crystallized Ligand	4.31 ± 0.00	78.31 ± 1.19

Note: Values are represented as mean ± SEM measured in angstrom units (Å). RMSD: root mean square deviation; RMSF: root mean square fluctuation; RoG: radius of gyration; MolSA: molecular surface area; SASA: solvent-accessible surface area.

Root Mean Square Deviation (RMSD):

A key measure for evaluating the structural stability and convergence of a protein-ligand system during molecular dynamics (MD) simulations is Root Mean Square Deviation (RMSD). Based on the variations of the C-α backbone atoms, the RMSD calculations offer information about the protein's conformational changes and the stability of ligand binding over time (35). Lower RMSD values imply minimal deviation, which corresponds to a more stable protein structure, whereas larger RMSD values show more atomistic deviations, which may signal structural instability (36). According to Table 9, the apo state of FGFR2 in this study had an RMSD of 1.36 ± 0.01 Å, which established a baseline for stability. Of the compounds that were analyzed, vitexin had the lowest RMSD value (1.15 ± 0.01 Å), indicating superior structural stability and minimal deviation from the reference structure throughout the simulation; on the other hand, quercetin (1.72 ± 0.01 Å) and isovitexin (1.80 ± 0.02 Å) had the highest RMSD values, indicating greater conformational flexibility or possible structural instability. These results show that vitexin is the most stable compound when compared to derazantinib.

Root Mean Square Fluctuation (RMSF):

Root Mean Square Fluctuation (RMSF) provides information on how ligand binding affects protein dynamics by quantifying the flexibility of individual residues within a protein during MD simulations (37). Finding areas with notable structural changes that may impact the stability and functionality of the protein is made easier with the use of RMSF analysis. Rigid, stable zones are indicated by lower RMSF values, whereas higher values imply more flexibility (36). According to Table 9, the apo state had an RMSF of $1.01 \pm 0.08 \text{ \AA}$, which served as a reference point. Of the ligands, quercetin had the highest flexibility ($1.06 \pm 0.10 \text{ \AA}$), which indicated significant residue fluctuations throughout the simulation; fenugreekine had an RMSF of $0.96 \pm 0.05 \text{ \AA}$, which indicated stable residue interactions and few fluctuations; and derazantinib had the lowest RMSF ($0.86 \pm 0.05 \text{ \AA}$), which indicated a stable conformation with little residue movement. These findings imply that derazantinib may be better at maintaining its structural integrity, while quercetin's greater flexibility may affect its binding performance and stability.

Radius of Gyration (RoG):

According to (36), the Radius of Gyration (RoG) is a measure of a protein structure's compactness throughout the simulation. A low RoG value denotes a tightly folded, stable structure, whereas a large RoG value suggests an extended, perhaps less stable conformation. Effective ligand binding and preserving a protein's physiological activity depend on structural compactness. According to Table 10 of this investigation, the compounds with the lowest RoG values were vitexin ($3.81 \pm 0.00 \text{ \AA}$) and quercetin ($3.74 \pm 0.00 \text{ \AA}$), which may indicate that they support the maintenance of a stable and compact protein structure. Fenugreekine showed balanced structural compactness with a modest RoG ($5.33 \pm 0.01 \text{ \AA}$). On the other hand, derazantinib had the greatest RoG value ($6.16 \pm 0.02 \text{ \AA}$), suggesting a longer conformation that would jeopardize stabilization. The promise of quercetin and vitexin as stable binding options is reinforced by their lower RoG values, which is beneficial for drug development tactics.

Solvent-Accessible Surface Area (SASA):

By measuring a protein's surface area exposed to a solvent, Solvent-Accessible Surface Area (SASA) can reveal how much its structure changes when a ligand binds to it (1). In this study, as indicated in Table 10, the standard drug derazantinib had the highest SASA ($235.00 \pm 3.22 \text{ \AA}^2$), reflecting substantial solvent exposure and potential structural flexibility, while quercetin ($30.00 \pm 0.77 \text{ \AA}^2$) and vitexin ($32.78 \pm 0.71 \text{ \AA}^2$) had the lowest SASA values, suggesting they maintain

compact structures with reduced solvent exposure. These results suggest that derazantinib may result in a less stable protein-ligand complex under solvent conditions, while quercetin and vitexin have better binding stability. The stability of vitexin and the compact nature of quercetin suggest that they could be promising drug candidates for FGFR2-targeted therapies. The combined analyses of RMSD, RMSF, RoG, and SASA offer a thorough evaluation of the structural stability and flexibility of FGFR2 upon ligand binding.

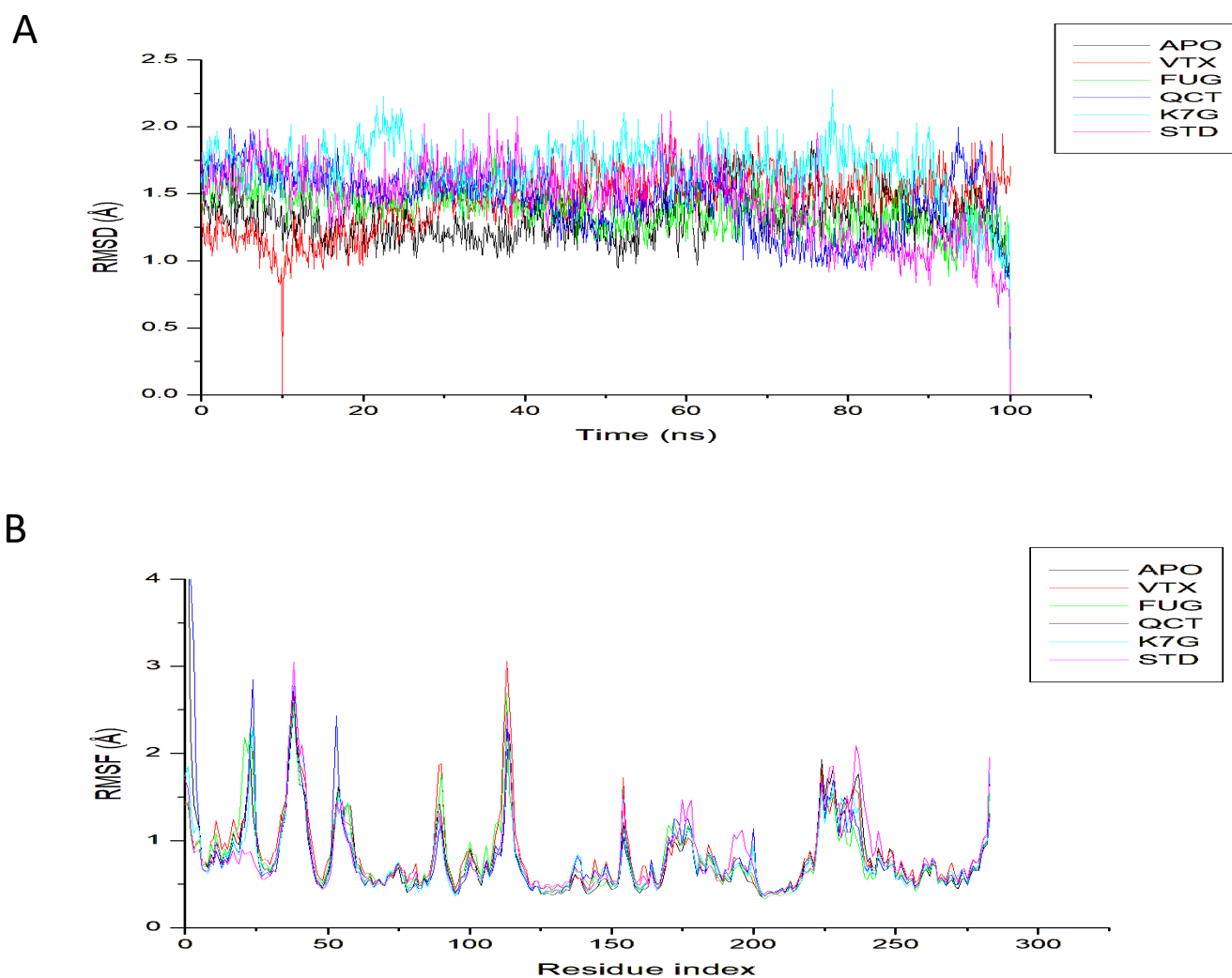
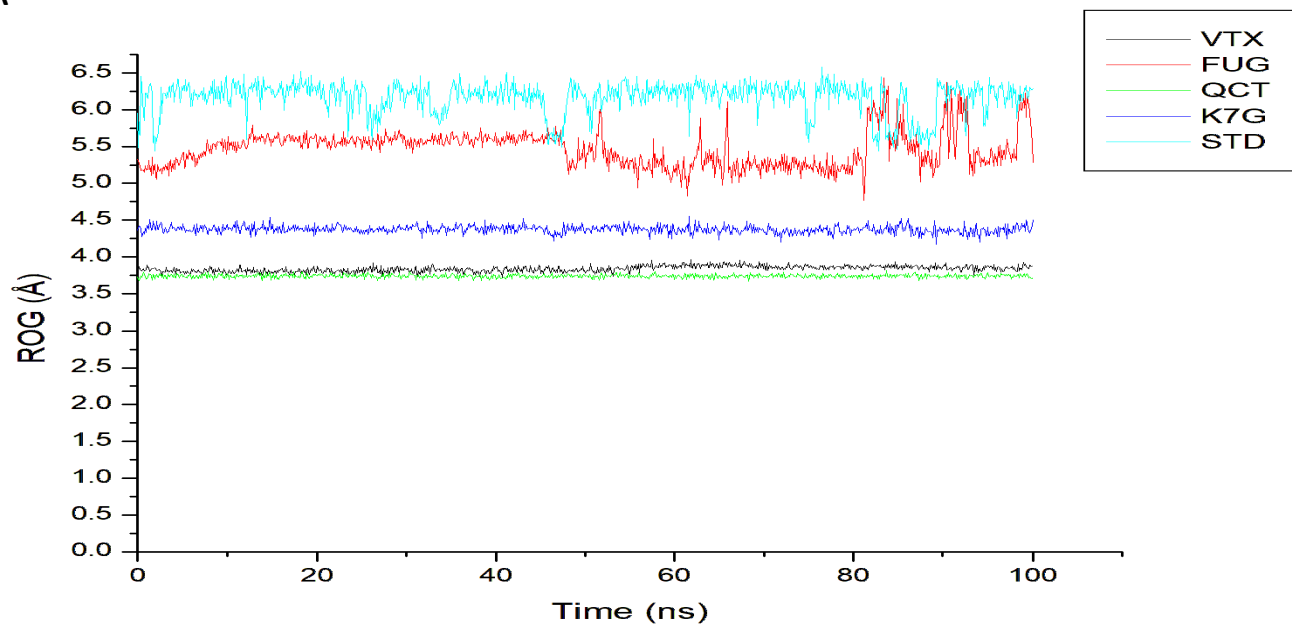


Fig. 8a: RMSD (A) and RMSF (B) plots of the selected ligands complexed with FGFR2.

A



B

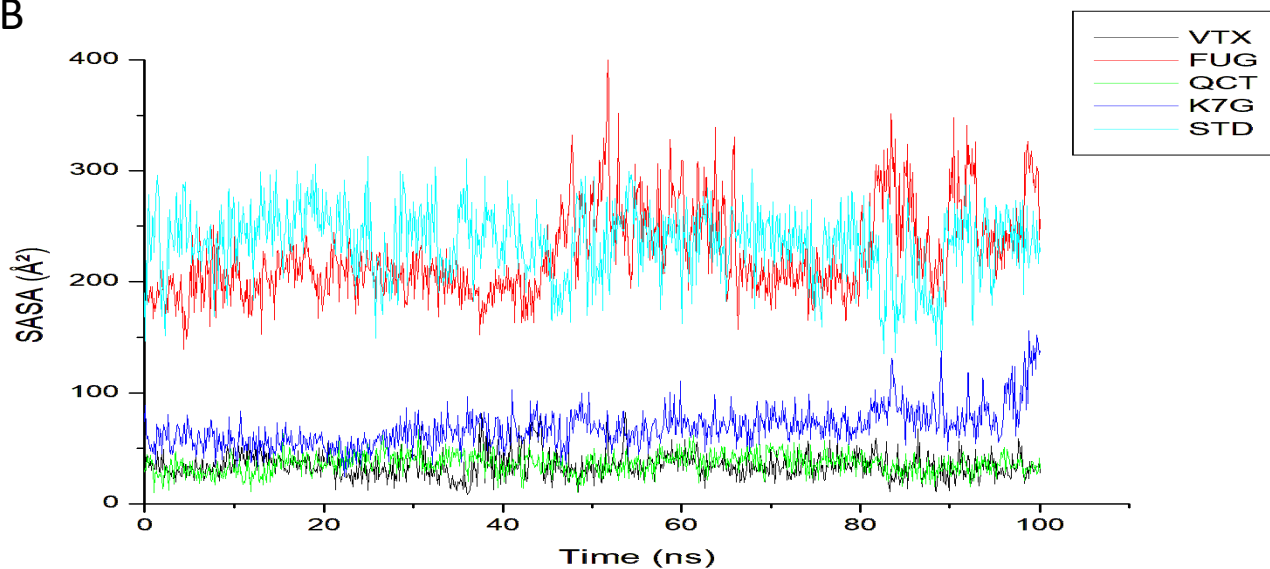


Fig. 8b: RoG (A) and SASA (B) plots of the selected ligands complexed with FGFR2

Conclusion

Medicinal plants have been a veritable source of drugs for the prophylaxis and treatment of diseases. *Trigonella foenum-graecum* (Fenugreek) has demonstrated numerous biological activities including antibacterial, antidiabetic, hepatoprotective, and anticancer effects. The current *in silico* study investigated the potential of fenugreek-derived phyto-compounds as inhibitors of FGFR2 a critical target in cancer therapy. Computational techniques including molecular docking, molecular dynamics (MD) simulations, and quantitative structure-activity relationship (QSAR) analysis were integrated to identify and characterize potential FGFR2 inhibitors among fenugreek phytochemicals. Docking studies revealed that vitexin exhibited the highest binding affinity (-13.35 kcal/mol), indicating strong interactions with FGFR2. MM/GBSA-based binding free energy furthermore revealed fenugreekine as the compound with the most favorable binding energy (-78.55 kcal/mol), outperforming the reference drug derazantinib (-75.25 kcal/mol). MD simulations further provided insights into the stability and dynamics of the protein-ligand complexes. RMSD analysis showed that vitexin maintained a stable conformation throughout the simulation, while RMSF analysis highlighted that derazantinib exhibited minimal residual movement, indicating enhanced structural integrity. Radius of Gyration (RoG) and Solvent-Accessible Surface Area (SASA) analyses further supported these findings, with vitexin and quercetin demonstrating compact structures and limited solvent exposure, which are advantageous for ligand stability. Overall, this study highlights the potential of fenugreek-derived compounds for FGFR2-targeted therapies. While the findings of this *in silico* study are promising, more *in silico* and *in vitro* studies are required to validate the identified compounds for efficacy and safety.

DECLARATION:

Ethics Approval and Consent to Participate:

Not applicable.

Consent to publication:

Not applicable.

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The authors received no specific funding for this work.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article.

COMPETING INTERESTS

The authors declare that they have no competing interest.

AUTHORS' CONTRIBUTIONS

K.T.M.: conceptualized the study, wrote the original draft, and contributed to the methodology.

P.C.O., M.S.M, S.Y.J.: contributed to formal analysis, reviewing, and conceptualization.

I.H.Y, S.O.E, E.O.O.: were responsible for methodology and formal analysis.

D.S.B., S.O.A.: performed visualization, validation, result analysis, and contributed to editing and reviewing the manuscript.

Y.A.A., E.A.A.: contributed to validation, result analysis, and reviewing the manuscript.

A.A.O.: contributed to editing and reviewing the manuscript.

O.B.A.: contributed to reviewing.

W.M.O.: performed visualization and validation

O.I.O., M.N.FO.: supervised the project and provided validation.

A.S.A., O.S.D.: contributed to the result analysis, and reviewing the manuscript.

All authors have read and approved the final manuscript.

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