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Multi-Target Interaction of Cymbopogon citratus Stapf and Cassia auriculata Linn Phytoconstituents in Epilepsy: An Integrated Molecular Docking, Dynamics, and MM/GBSA Study

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ABSTRACT: Background: Epilepsy is a complex neurological disorder characterised by dysregulated neuronal signalling, oxidative stress and neuroinflammation. The current AEDs have some limitations, such as drug resistance and side-effects, and thus the search for novel multi-target therapeutic agents is obligatory. The phytoconstituents of Cymbopogon citratus Stapf viz citral, neral, linalool and Cassia auriculata Linn viz apigenin, kaemferol, rutin, quercetin was evaluated in this study as possible antiepileptic modulators by integrated computational analyses.

Methods: Molecular docking was carried out with the epilepsy-related targets glycine receptor (PDB ID: 6UBS) and GABAA receptor (PDB ID: 4COF). The lead compounds linalool and apigenin were then further studied using 100 ns molecular dynamics simulation, binding free energy using MM/GBSA, energy decomposition analysis, and ADMET profiling.

Results: Docking scores for selected phytoconstituents were found to be ranging from -1.12 to -5.52 kcal/mol that showed favourable binding affinity of linalool and apigenin with both the targets. To assess the stability of the protein–ligand interactions, the molecular dynamics simulations were performed for 100 ns showing stable RMSD and RMSF profiles. The stability of these bindings was obtained from MM/GBSA analysis and was found to be high in both cases with ΔG bind of -40.66 and -40.53 kcal/mol in the cases of 4COF and 6UBS, respectively.

Conclusion: The results suggest that phytoconstituents of Cymbopogon citratus Stapf and Cassia auriculata linn are potential candidates for epilepsy therapeutic applications and are shown to exhibit favourable ADMET properties while interacting with a number of receptors.

1. INTRODUCTION

Epilepsy is a chronic brain disease defined by recurrent, spontaneous seizures caused by excessive, abnormal and synchronous electrical activity in neurons [1]. It affects over 50 million people globally and remains a serious health burden because of its multifactorial causes and debilitating effects on the patient's quality of life [2]. Pathophysiology of epilepsy is a complex interaction of factors, such as dysfunction of ion channels, imbalance of excitatory and inhibitory neurotransmission, oxidative

stress, neuro-inflammation, and changes in synaptic plasticity [3]. Specifically, dysfunction of γ -aminobutyric acid (GABA)-ergic inhibition and increased glutamatergic excitation are well known to play a pivotal role in the genesis and spread of seizures [4].

While a range of antiepileptic drugs (AEDs) are now available, nearly one-third of epilepsy cases are resistant to pharmacotherapy, reducing its therapeutic efficacy [5-6]. There is a renewed interest in the use of natural products as a source of new lead compounds because of their structural diversity, biocompatibility and capacity to interact with multiple targets [7-8]. Herbal medicines have been traditionally used in various countries for the treatment of neurological diseases such as parkinsonism, schizophrenia and epilepsy [9-10].

Cassia auriculata Linn (Tanner's cassia) and *Cymbopogon citratus* Stapf (Lemongrass) contain phytoconstituents, including flavonoids, terpenoids, alkaloids and phenolic compounds that have shown potential anticonvulsant properties through modulation of the neurotransmitters and reduction of oxidative and inflammatory damage [11].

The drug discovery process has recently evolved from the "one drug-one target" approach to a more comprehensive approach called polypharmacology, which focuses on the interaction of drugs with multiple targets [12]. This concept is especially pertinent for a complex disease like epilepsy, where multiple pathways and networks are involved in the disease process [13]. Phytochemicals, which are often present as a mixture, are well aligned to this paradigm and may have synergistic or additive effects when interacting with multiple targets. This may occur when multiple compounds bind to different sites on a protein or to different proteins, thus complementing each other's actions [14-15].

The development of computational methods has greatly streamlined drug discovery. Computer-aided drug design (CADD) offers an efficient and cost-effective approach to discover and optimise drug-like molecules [16]. The binding mechanism and affinity of ligands in the target protein's binding pocket are frequently examined using molecular docking, which provides details on the binding interactions [17]. But docking studies are limited to a static view of the interaction between ligands and proteins and may not provide a comprehensive insight into the dynamics of the biological system [18]. To overcome these drawbacks, molecular dynamics (MD) simulations are applied to assess time-dependent properties, stability and dynamics of protein-ligand complexes in a physiological environment [19]. MD simulations can yield insights into stability, flexibility, and temporal persistence of interactions, and allow a better interpretation of docking results [20]. Moreover, binding free energy calculations using the Molecular Mechanics Born Surface Area (MM/GBSA) approach allow for the quantitative estimation of binding strength and help to enhance the predictive power in drug design research [21]. Recent research has shown the successful use of integrated computational methodology, involving docking, molecular dynamics, and binding free energy calculations, to discover possible leads against epilepsy targets [22-23]. There is a gap in comprehensive studies on the multi-target therapeutic effects of phytoconstituents from *Cymbopogon citratus* Stapf and *Cassia auriculata* Linn using an integrated *in silico* approach [24].

Thus, this study focuses on investigating the multi-target antiepileptic effects of the phytoconstituents of these herbal medicines using integrated computational approaches. We employed molecular docking to assess binding affinity and interactions with epilepsy-related target proteins, and molecular dynamics simulations to predict stability and dynamic behaviour. Additionally, MM/GBSA calculations were carried out to assess the binding free energy. The findings of this study will offer valuable insights at a molecular level into possible synergies and inform the development of potent phytopharmaceuticals for the treatment of epilepsy [25].

The study design and workflow of the present study is summarised in the Figure.1, where phytoconstituents from *Cymbopogon citratus* Stapf and *Cassia auriculata* Linn were investigated for antiepileptic potential. A series of natural compounds were docked into various protein targets linked to epilepsy, followed by molecular dynamics simulations to study the stability and dynamics of protein-ligand complexes in a physiological environment. The binding free energies of the complexes were also calculated using the MM/GBSA method. The findings reveal strong protein-ligand interactions, minimal structural fluctuations and promising binding energetics, suggesting the phytoconstituents investigated in this study are likely to have a high potential as multi-target antiepileptic drug candidates [26].

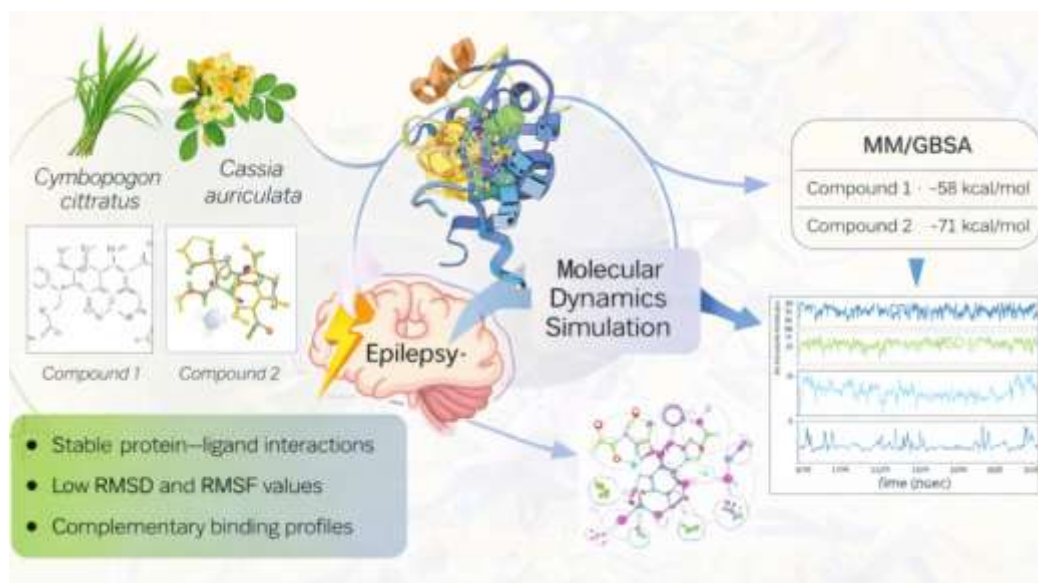


Figure 1. workflow of the present study

2. METHODOLOGY

2.1. Computational Tools and Software

The computational research was done using the Schrödinger suite (Schrödinger, LLC, New York, USA; release 2023-1). The Glide module was used for molecular docking, and the Desmond program was used for molecular dynamics (MD) simulations, RMSD and RMSF analysis. MM/GBSA calculations were performed using the Prime module. Visualizations and interaction assessments were done with Discovery studio visualizer.

2.2. Protein and Ligand Preparation

The protein production wizard in the Schrödinger suite (Release 2023-1) was used to generate the three-dimensional crystal structures of target proteins linked to epilepsy that were obtained from the Protein Data Bank (PDB). Protein preparation included bond order assignment, hydrogen addition, removal of crystallographic water molecules beyond 5 Å, completion of missing residues using Prime, protonation state assignment at pH 7.0 ± 0.2 with Epik, hydrogen-bond optimization, and restrained energy minimization using the OPLS4 force field. Phytoconstituents of *Cymbopogon citratus* Stapf and *Cassia auriculata* Linn were selected from the literature, retrieved from the PubChem database, and prepared using LigPrep by generating ionization states (pH 7.0 ± 2.0), relevant stereoisomers, geometry optimization, and up to 32 low-energy conformers using the OPLS4 force field [27].

2.3. Molecular Docking

The Glide grid generation module was utilized to generate the receptor grid by placing the grid box at the site of the co-crystallized ligand with a size of $20 \times 20 \times 20$ Å was used to cover the entire binding site. While generating the grid, the van der Waals radii scaling factor was set to 1.0 with a partial charge cut-off of 0.25, and no constraints were applied. Docking calculations were carried out using the Glide program in 'Standard Precision' (SP) mode. The ligands were docked flexibly, while the receptor remained rigid. The van der Waals radii scaling factor for the ligands was 0.80, partial charge cut off was 0.15, and maximum number of poses generated was 10. The final pose was chosen for each ligand based on the Glide Score and interaction analysis. Important intermolecular interactions (hydrogen bonding, hydrophobic interactions, π - π stacking and electrostatic interactions) were analysed to determine the binding affinity and stability of the ligands in the active site [28].

2.4. ADMET and Drug-Likeness Analysis

The QikProp program of Schrödinger suite was employed to predict the physicochemical and pharmacokinetic properties of the selected phytoconstituents to assess their drug-likeness and potential as drug candidates. The parameters considered included the Lipinski's Rule of Five for oral drug-likeness, octanol/water partition coefficient (log P) and aqueous solubility

(log S) for assessing lipophilicity and solubility. Absorption and permeability were determined by predicted Caco-2 cell permeability and human oral absorption. Central nervous system (CNS) penetration was predicted based on log BB values to determine blood–brain barrier (BBB) permeation, an important consideration for potential antiepileptic drugs. Furthermore, predicted HERG channel inhibition was used to assess potential cardiotoxicity. These metrics allowed a holistic view of the pharmacokinetic properties and safety of the chosen compounds [29].

2.5. Molecular Dynamics Simulation (MD)

The Desmond module of the Schrödinger Suite was used to perform MD simulations in order to investigate the stability of protein–ligand interactions. Each system's orthorhombic TIP3P water boxes held a 10 Å buffer that had been neutralized with ions of Na⁺/Cl[−] at a concentration of 0.15 M NaCl. Using the Nose–Hoover thermostat and Martyna–Tobias–Klein barostat with an integration time step of 2 fs in the NPT ensemble, 100 ns production simulations were carried out at 300 K and 1 atm following energy minimization and default equilibration. Trajectory analysis was performed using the simulation interaction diagram module to analyze the RMSD of the protein and the ligand, RMSF of the residues, radius of gyration, secondary structure stability, hydrogen bond occupancy, and protein–ligand interaction profile (hydrogen bonding, hydrophobic, ionic, water-bridge interactions) [30].

2.6. Binding Free Energy Calculation (MM/GBSA)

The Prime MM/GBSA module was used for the binding free energy calculations.

The binding free energy (ΔG_{bind}) was calculated as:

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

Where, G_{complex} , G_{protein} and G_{ligand} represent minimized energies of the complex, protein and ligand, respectively.

The binding free energy was further broken down into individual components, such as van der Waals & electrostatic forces, polar and non-polar solvation, to gain insights into the binding interactions. In order to improve the precision of the calculations, snapshots were taken from the MD simulations at regular time intervals and the MM/GBSA calculations were performed. This ensures that conformational sampling is taken into account, and thus gives a better estimate of binding free energy than calculations based on single snapshots [31].

2.7. Synergistic Interaction Analysis

We conducted a comparative analysis of phytoconstituents from *Cymbopogon citratus* Stapf and *Cassia auriculata* Linn to explore potential multi-target interactions and synergism at the molecular level. This study involved a comparative evaluation of docking scores, molecular dynamics stability measures and MM/GBSA binding free energy. Beyond individual binding scores, interaction maps of key compounds were analysed to determine the complementary binding patterns within the active site of the protein target & the capacity of ligands to engage with different residues or binding pockets, which may improve the overall stability of protein–ligand complex, as well as modulate its function. This comprehensive approach allowed the detection of potential multi-target and synergistic interactions [32].

3. RESULT AND DISCUSSION

3.1. Protein and ligand preparation

The optimized protein structures (PDB IDs: 6UBS and 4COF) were prepared with the appropriate protonation states and without steric clashes, and reliable models for computational analysis were obtained. Prior to docking, the selected phytoconstituents (linalool, apigenin, rutin, kaempferol, citral, neral, and quercetin) were optimized to their lowest energy conformation and physiologically relevant ionization states. The refined protein–ligand complexes allowed for correct evaluation of binding interactions, whereas the structural diversity of the selected phytoconstituents allowed to assess different binding interaction profiles with the target proteins in molecular docking and molecular dynamics simulations.

3.2. Molecular docking

3.2.1. Target Analysis of 6UBS

The binding affinity of the selected phytoconstituents against the target protein (PDB ID: 6UBS) were studied using molecular docking analysis. 6UBS is a glycine receptor which is a member of ligand gated ion channel family particularly acts as inhibitory neurotransmission. All the docking results of the screened compounds are enumerated in Table 1, with binding affinities varying from -1.40 to -3.93 kcal/mol. Compound like tropine ester (CID 3000322) showed relatively higher binding affinity with docking scores of -3.83 kcal/mol. However, the main phytoconstituents of *Cymbopogon citratus* Stapf, Linalool (CID: 638011), Neral (CID: 643779), Citral (CID: 638011) exhibited favourable binding affinity, with a docking score of -3.05 kcal/mol, -2.37 kcal/mol, -2.35 kcal/mol respectively. Further docking (Table 2) also showed compound Apigenin (CID: 5280443) to be the most potent ligand with the highest binding affinity (docking score -5.52 kcal/mol). This compound showed much better interaction energy than other ligands, suggesting a more stable binding within the active site. In conclusion, the comparative docking analysis (Tables 1 and 2) suggests that compound 5280443 has higher binding affinity, whereas Linalool has favourable hydrophobic interactions.

Table 1. Docking scores, glide score and energy parameters of screened phytoconstituents against the target protein.

Molecule (CID)	Docking Score (kcal/mol)	Glide Gscore	Glide Energy	van der Waals (evdw)	Electrostatic (ecoul)
3000322	-3.833	-4.055	-21.979	-20.124	-1.856
5280805	-1.996	-3.804	-34.438	-31.216	-3.223
5280863	-1.674	-3.433	-14.660	-11.579	-3.082
643779	-2.374	-2.374	-15.436	-15.499	0.063
638011	-2.352	-2.352	-16.217	-16.048	-0.170
5280343	-1.404	-3.163	-15.606	-12.153	-3.452

Table 2. Docking comparison of some high-affinity compounds against the target protein (PDB ID: 6UBS) based on binding energy contributions.

Molecule (CID)	Docking Score (kcal/mol)	Glide Gscore	Glide Energy	van der Waals (evdw)	Electrostatic (ecoul)	Emodel
5280443	-5.524	-5.572	-26.562	-22.199	-4.363	-33.978
6549	-3.053	-3.053	-17.403	-15.038	-2.365	-19.785

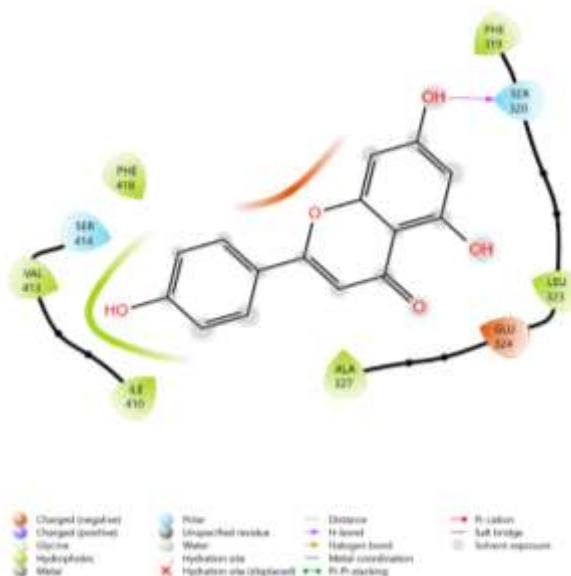


Figure 2 . Interaction diagrams of compounds Apigenin (CID: 5280443) bound to the target protein (PDB ID: 6UBS).

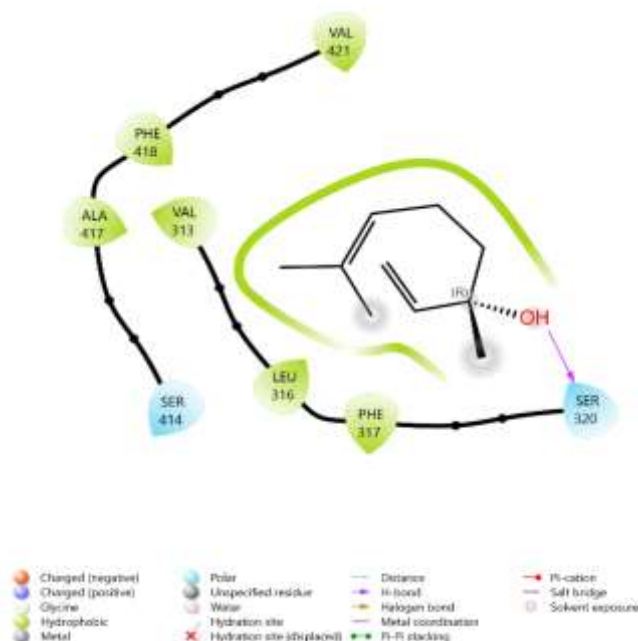


Figure 3 . Interaction diagrams of compounds Linalool (CID: 6549) bound to the target protein (PDB ID: 6UBS).

The interaction of key compounds with the active site of the target protein is depicted in Figures 2. Apigenin with the highest binding affinity displayed a robust interaction network with residues such as SER320, GLU324, LEU323, ALA327 and hydrophobic residues such as PHE and VAL. A strong hydrogen bond interaction with SER320, in addition to a number of hydrophobic interactions, resulted in increased stability of the protein ligand complex. On the other hand, Linalool (Figure 3) exhibited a more limited number of interactions, reflected in the moderate docking score. A hydrogen bond with SER320 and hydrophobic contacts with residues VAL313, LEU316, PHE317, PHE418 and VAL421 were observed. The Apigenin had the most favourable interaction profile which was in line with its best docking score and binding free energy.

3.2.2. 4COF Target Analysis

Molecular docking was carried out to determine the binding score of screened phytoconstituents against the target protein (PDB ID: 4COF). 4COF is a human GABA A receptor which plays critical role in inhibitory neurotransmission and regulation

of neuronal excitability. Docking scores of all the molecules screened are listed in Table 3 and vary from -1.13 to -2.43 kcal/mol. Tropine ester (CID: 3000322) showed comparatively favourable binding affinity with a docking score of -2.43 kcal/mol followed by neral (CID: 643779) with a docking score of -2.04 kcal/mol. On the other hand, a major phytoconstituent of *Cymbopogon citratus* Stapf, linalool, had lower binding affinity, with a docking score of -1.63 kcal/mol. Further docking analysis (Table 4) also reveals that apigenin is the most promising ligand with the highest binding affinity with a docking score: -4.05 kcal/mol. However, the comparative docking studies which is depicted in Tables 3 and 4, suggests that apigenin has a higher binding affinity with 4COF target protein the 2D interaction diagram of apigenin and linalool in complex with the target protein (PDB ID: 4COF) is shown in Figure 4 and 5.

Table 3. Molecular docking results of screened phytoconstituents against the target protein (PDB ID: 4COF).

Molecule (CID)	Docking Score (kcal/mol)	Glide Gscore	Glide Energy	van der Waals (evdw)	Electrostatic (ecoul)
3000322	-2.434	-2.656	-24.624	-20.353	-4.271
643779	-2.047	-2.047	-18.876	-14.543	-4.333
5280805	-1.905	-3.713	-40.037	-21.927	-18.110
5280863	-1.846	-3.605	-23.725	-19.276	-4.448
5280343	-1.804	-3.562	-25.935	-17.615	-8.321
638011	-1.128	-1.128	-20.015	-16.513	-3.501

Table 4. Molecular docking results of selected high-affinity compounds against the target protein (PDB ID: 4COF).

Molecule (CID)	Docking Score (kcal/mol)	Glide Gscore	Glide Energy	van der Waals (evdw)	Electrostatic (ecoul)	Emodel
5280443	-4.049	-4.097	-26.701	-17.897	-8.804	-33.867
6549	-1.630	-1.630	-17.478	-13.182	-4.296	-17.996

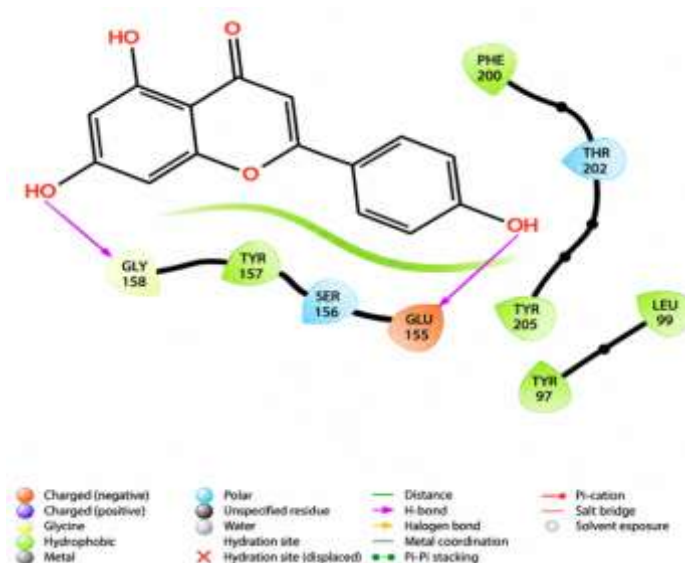


Figure 4. 2D interaction diagram of apigenin in complex with the target protein (PDB ID: 4COF).

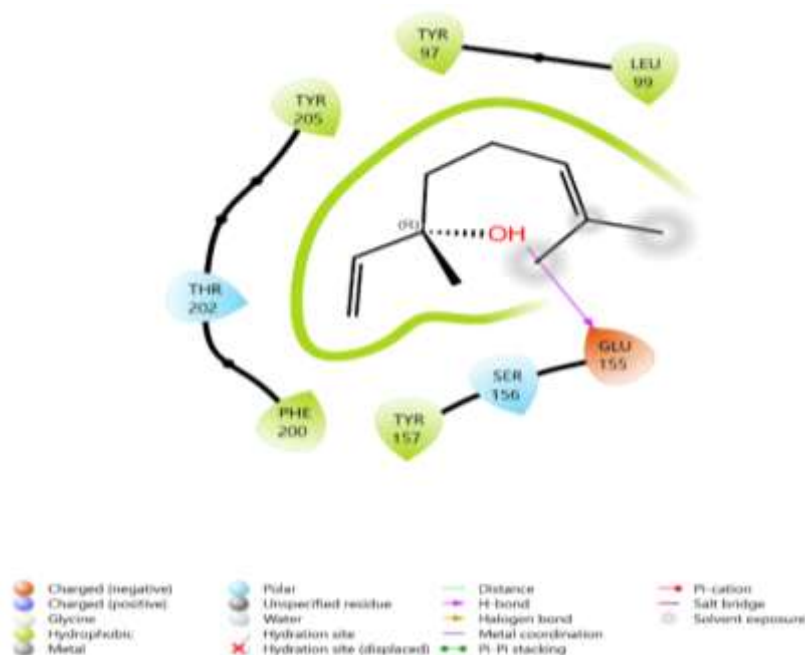


Figure 5. 2D interaction diagram of linalool in complex with the target protein (PDB ID: 4COF).

3.2.3. Multi-target Synergistic Interaction Analysis

The interaction analysis from molecular docking study was also carried out to verify complementary nature of the compounds. The ligand in 6UBS is bound to the active site by several hydrophobic and hydrogen bonding interactions, but they are not well positioned and well organised, leading to the moderate stability of the ligand in the binding site. In 4COF, the interaction network is densely packed. The ligand makes extensive hydrophobic interactions and hydrogen bonds with key residues (ASP411, SER320, GLU324 and PHE317), thus promoting more stability in the binding pocket. In comparison, 6UBS enables the binding of the ligand but has a moderate interaction network and 4COF has more stable and favourable interaction. The results indicate that molecules that have hydrophobic parts (with linalool-like characteristics) and molecules that are good at forming hydrogen bonds (with apigenin-like core) might cooperate to strengthen the interaction with the binding site and the possibility of synergistic activity as shown in figure 6.(3D Protein-ligand interactions of 6UBS and 4COF)

Table 5. Comparative docking scores and energy parameters of selected phytoconstituents against target proteins (PDB IDs: 6UBS and 4COF).

Molecule (CID)	Docking Score (6UBS)	Docking Score (4COF)	Glide Gscore (6UBS)	Glide Gscore (4COF)	Glide Energy (6UBS)	Glide Energy (4COF)
5280443	-5.524	-4.049	-5.572	-4.097	-26.562	-26.701
3000322	-3.833	-2.434	-4.055	-2.656	-21.979	-24.624
643779	-2.374	-2.047	-2.374	-2.047	-15.436	-18.876
5280805	-1.996	-1.905	-3.804	-3.713	-34.438	-40.037
5280863	-1.674	-1.846	-3.433	-3.605	-14.660	-23.725
5280343	-1.404	-1.804	-3.163	-3.562	-15.606	-25.935
638011	-2.352	-1.128	-2.352	-1.128	-16.217	-20.015
6549	-3.053	-1.630	-3.053	-1.630	-17.403	-17.478

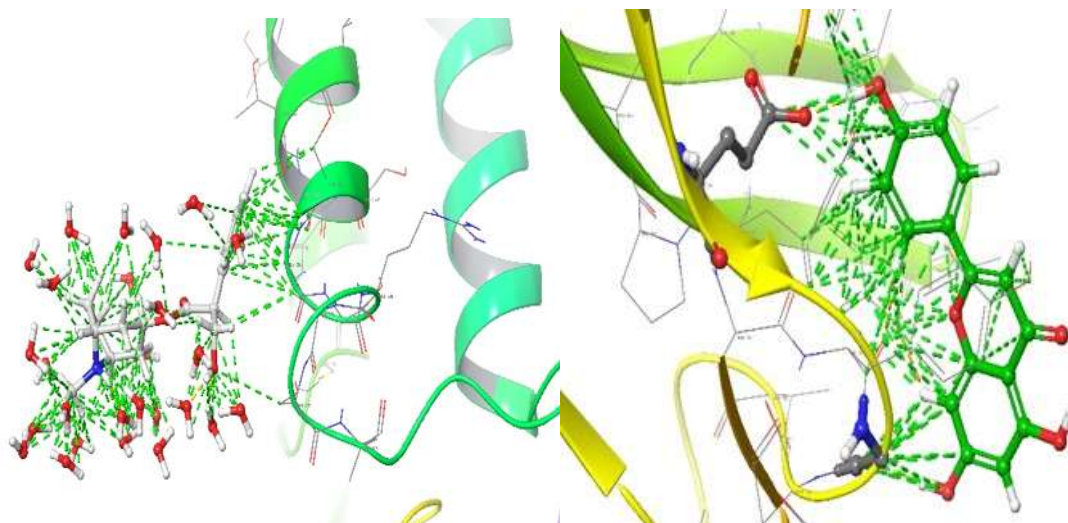


Figure 6. A.3D Protein-ligand interactions of 6UBS

B. 3D Protein-ligand interactions of 4COF.

3.2.4. Physicochemical and ADMET Properties

The comparative properties of the lead compounds apigenin (CID: 5280443) and linalool (CID: 6549) are shown in Table 6, while the screening of other phytoconstituents is shown in Table 7. The lead compounds adhered to Lipinski's Rule of Five, suggesting good oral absorption and promising pharmacological potential as drug-like compounds. The molecular weight of apigenin was 270.24 g/mol, while that of Linalool was 154.25 g/mol, which is typically linked with high permeability and absorption. The predicted lipophilicity (QPlogPo/w) of 1.605 and 3.142 for apigenin and linalool, respectively, is within the acceptable range for oral drugs, indicating a suitable balance between hydrophilicity and lipophilicity. Likewise, the aqueous solubility (QPlogS) values suggest that both compounds have suitable solubility for biological studies.

Table 6. Physicochemical and ADMET properties of selected compounds.

Property	CID: 5280443	CID: 6549
Molecular Weight (g/mol)	270.24	154.25
Dipole	5.369	1.807
SASA (Å ²)	490.13	431.88
FOSA	0	358.90
FISA	204.27	29.07
PISA	285.85	43.90
H-bond Donors	2	1
H-bond Acceptors	3.75	0.75
QPlogPo/w	1.605	3.142
QPlogS	-3.332	-2.967
QPlogHERG	-5.114	-3.599
QPPCaco (nm/sec)	114.49	5250.61
QPlogBB	-1.446	0.015

QPPMDCK	47.53	2970.37
Human Oral Absorption (%)	73.19	100
PSA	99.76	18.70
Rule of Five Violations	0	0
#Metabolic Reactions	3	4

There were notable variations in the permeability between the two compounds. The Caco-2 permeability value of linalool which is 5250.61 nm/sec is much higher than that of apigenin with 114.49 nm/sec, suggesting improved absorption in the intestines. Accordingly, the predicted human oral absorption values linalool is 100% absorbed, while apigenin is moderately absorbed at 73.19%. This result is based on the data presented in Table 6.

For drug development, the penetration into the central nervous system (CNS) is an important factor for antiepileptic drugs. The calculated blood–brain barrier penetration (QPlogBB) values showed that linalool (0.015) is expected to penetrate the BBB more readily, suggesting better CNS activity. However, the QPlogHERG values for both compounds are in the safe range, indicating a reduced potential for cardiac toxicity. These results are validated by the polar surface area (PSA) which is much lower for linalool (18.69 Å²), reflecting its increased membrane permeability and BBB passage. Based on the ADMET analysis as depicted in Tables 6, & 7, linalool showed good pharmacokinetic results.

Table 7. QikProp-predicted physicochemical and ADMET properties of selected compounds.

Property	638011	5280863	643779	5280343	5280805	3000322
Molecular Weight (MW)	152.236	286.240	152.236	302.240	610.524	303.357
Dipole	5.403	5.195	5.467	6.039	6.419	5.764
SASA	432.232	506.215	428.860	518.008	849.904	542.445
FOSA	323.683	0	322.431	0	216.185	291.656
FISA	82.526	239.139	78.255	286.535	426.275	80.120
PISA	26.024	267.076	28.174	231.472	207.445	170.670
HBD	0	3	0	4	9	0
HBA	2	4.5	2	5.25	20.55	6.7
QPlogPo/w	2.314	1.041	2.328	0.368	-2.452	1.244
QPlogS	-2.710	-3.137	-2.646	-2.890	-2.757	-0.516
QPlogHERG	-3.632	-5.197	-3.570	-5.104	-6.098	-5.100
QPPCaco	1634.203	53.475	1793.929	18.997	0.899	429.562
QPlogBB	-0.392	-1.873	-0.348	-2.398	-5.024	-0.038
QPPMDCK	841.218	20.875	930.430	6.820	0.252	219.571
% Oral Absorption	100	63.972	100	51.987	0	81.353
PSA	37.884	120.746	37.707	142.433	270.873	71.293
#Metab	5	4	5	5	10	4
Rule of Five	0	0	0	0	3	0

SASA: Solvent Accessible Surface Area; FOSA: Hydrophobic Component of SASA; FISA: Hydrophilic Component of SASA; PISA: π (Pi) Component of SASA; QPlogPo/w: Predicted Octanol/Water Partition Coefficient; QPlogS: Predicted Aqueous

Solubility; QPlogHERG: Predicted IC₅₀ value for hERG channel inhibition; QPPCaco (nm/sec): Predicted Caco-2 Cell Permeability; QPlogBB: Predicted Brain/Blood Partition Coefficient; QPPMDCK: Predicted MDCK Cell Permeability; PSA: Polar Surface Area.

3.3. Molecular dynamics

3.3.1. Protein-Ligand RMSD Analysis

The structural stability of the protein-ligand complex was assessed by measuring the RMSD of the protein backbone and ligand across a 100-ns molecular dynamics simulation (Figure 7). The protein backbone RMSD elevated during the first equilibration phase and then stabilized with mild fluctuations, suggesting that the complex reached structural equilibrium and stayed steady throughout the simulation. This suggests that the protein-ligand complex maintained a stable binding conformation during the 100 ns simulation.

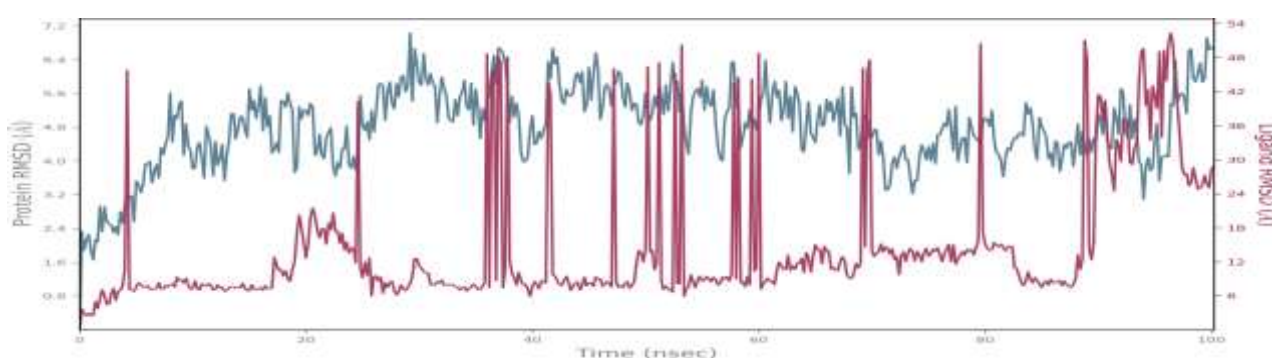
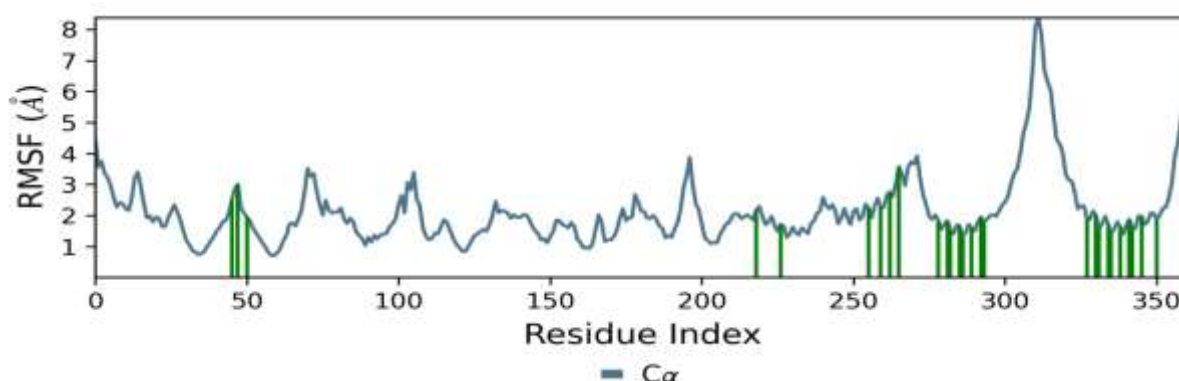


Figure 7. RMSD profiles of the protein backbone and ligand.

3.3.2. Protein RMSF Analysis

The protein's residue-wise flexibility and dynamics throughout the molecular dynamics simulation were analyzed using the root mean square fluctuation (RMSF) of the protein. The RMSF analysis showed (Figure 8) that the majority of residues had low fluctuations, suggesting the overall stability of the protein during the simulation. Hence with the expected flexibility of protein structures, the terminal regions (N- and C-terminal) and loop areas showed higher fluctuations than the secondary structures (α -helices and β -sheets). Notably, residues in and around the active site showed relatively lower RMSF values, suggesting that the protein-ligand interactions are maintained throughout the simulation. The low RMSF values of these residues direct that binding of the ligand may result in rigidification of the binding pocket. However, the RMSF analysis suggests that the protein remains rigid in important regions while being flexible in the expected regions.



Figure

8. RMSF of protein residues.

The flexibility of the protein at the residue level is depicted in Figure 3, with the majority of residues showing low fluctuation values, suggesting stability. Ligand RMSF (Figure. 9) also supports the stability of the ligand with low fluctuations among the atoms. This suggests the ligand retains its stable shape in the binding site but can flex slightly in non-essential parts of the molecule to optimise binding interactions.

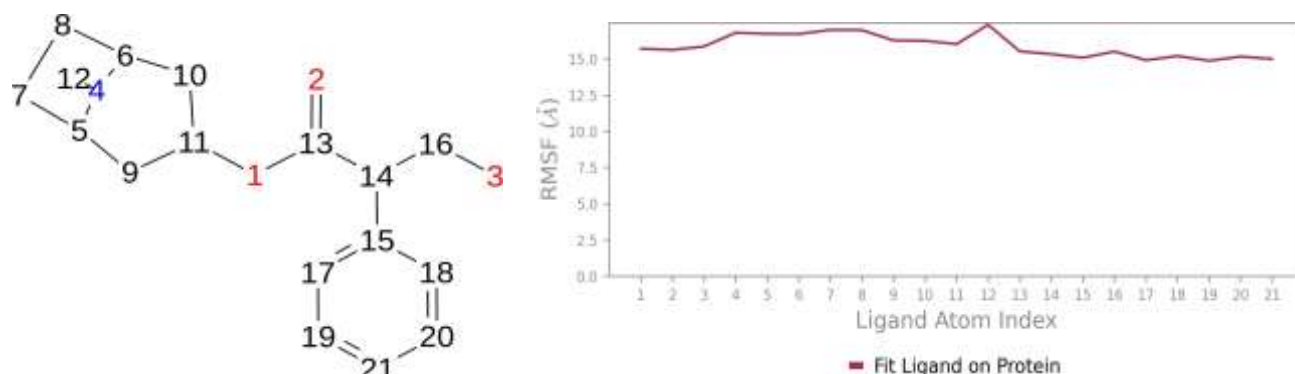


Figure 9. Ligand root mean square fluctuation (L-RMSF) profile.

3.3.3. Protein Secondary Structure Analysis

The molecular dynamics simulation of the protein for 100 ns showed that the overall secondary structure architecture remained unchanged during the simulation, as shown by secondary structure element (SSE) analysis (Figure 10 and 11). The protein was found to have 32.57% α -helices, 25.07% β -strands and 57.64% SSE. SSE distribution and time-dependent SSE profile showed little difference with no loss or change of α -helices or β -strands during the simulation.

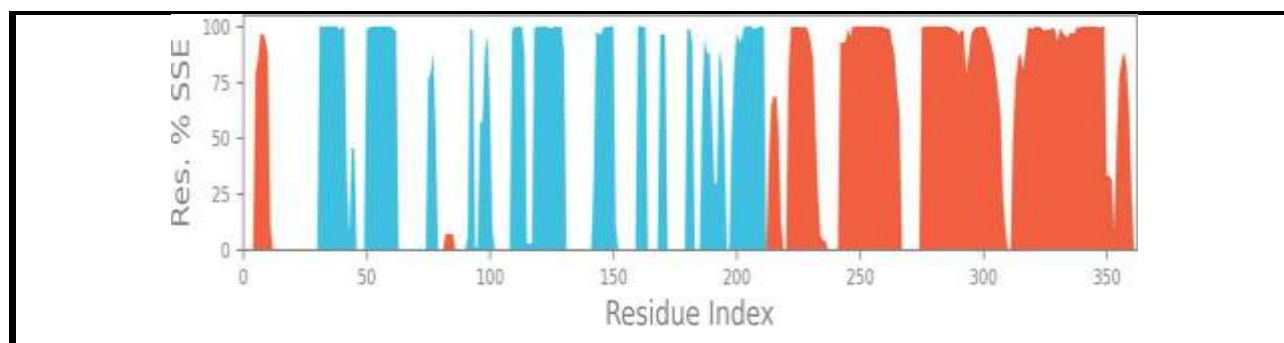


Figure 10. Residue-wise distribution of secondary structure elements (α -helices and β -strands).

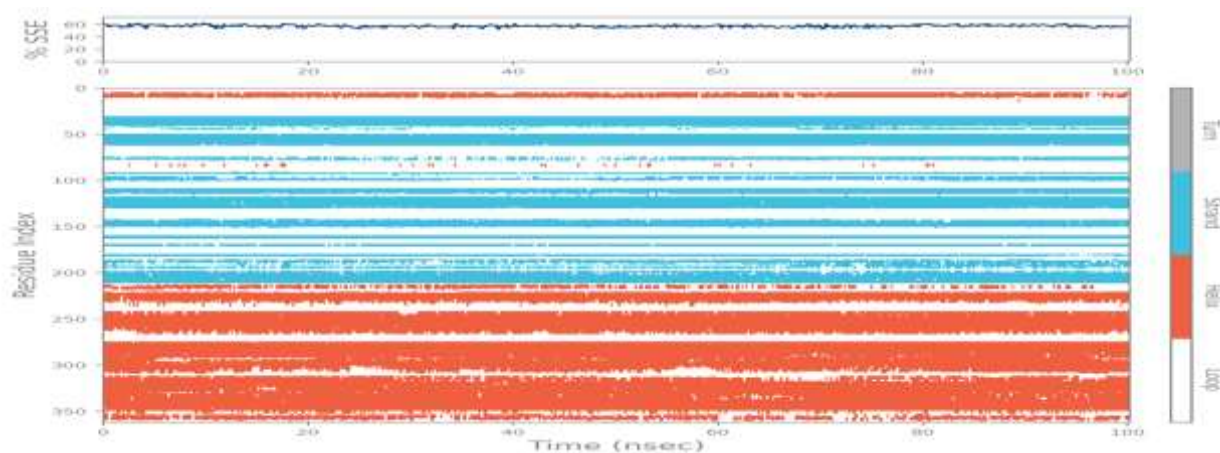


Figure 11. Time evolution of protein SSE during the simulation, demonstrating structural stability.

3.3.4. Protein-Ligand Interaction Analysis

Protein-ligand interactions were found to be stable and durable during the 100 ns molecular dynamics simulation (Figure 12). The percentage of time that several key residues interacted with the ligands was larger than 50% for the entire duration of the simulation, which suggests that the ligand remained in the binding site and that the binding was maintained. The complementary interaction profiles between the phytoconstituents of *Cymbopogon citratus* Stapf and *Cassia auriculata* Linn align with the suggested

synergistic target modulation which indicate the structural stability of the protein–ligand complexes and provide computational evidence for the synergistic therapeutic potential of the selected phytoconstituents for epilepsy.

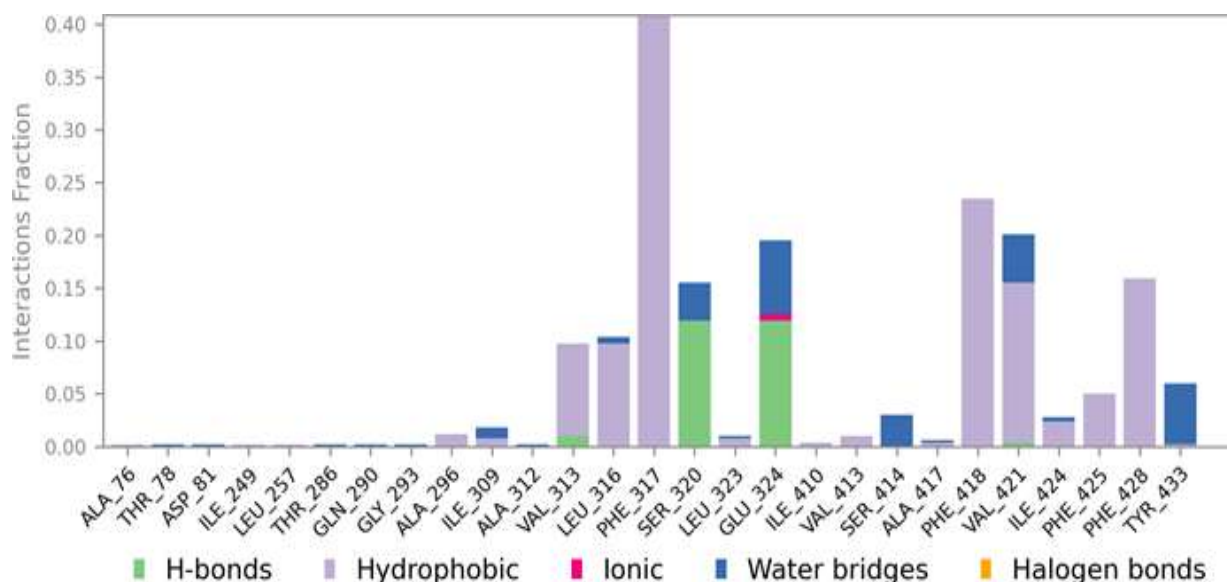


Figure 12. Time-resolved protein–ligand interaction profile, illustrating the persistence of hydrogen bonds, hydrophobic interactions, ionic interactions, and water bridges.

3.3.5. Ligand Torsion Profile Analysis

The torsional dynamics of apigenin in complex with 6UBS were analysed to investigate the conformational behaviour within the 100ns molecular dynamics simulation (MD) of the complex (Figure. 13). The probability distributions of the torsion angles were mostly limited to low-energy conformations, suggesting a minimal rotation around all the angles during the simulation. Small changes were seen for a few rotatable bonds but were between energetically favourable conformations and did not alter the overall binding geometry.

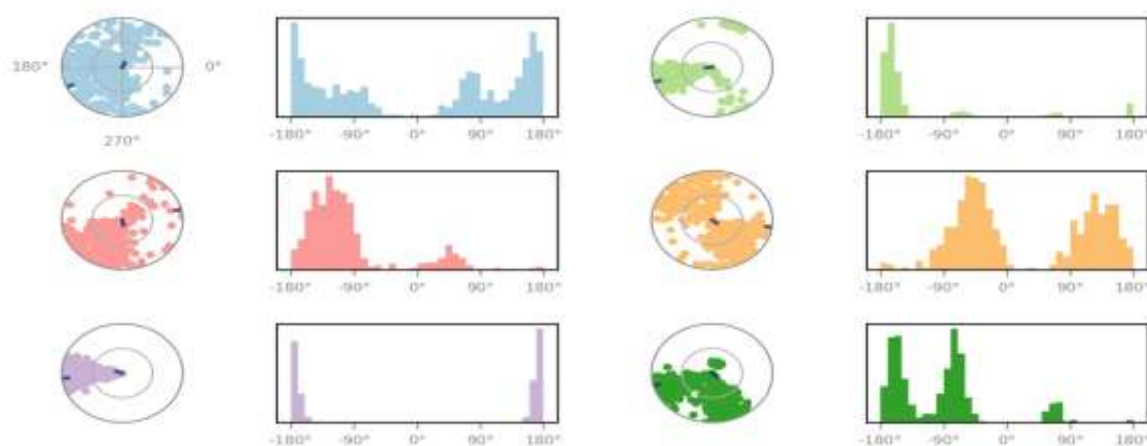


Figure 13. Torsional dynamics of apigenin in complex with 6UBS.

3.3.4. Ligand Properties Analysis

As illustrated in Figure 14, ligand RMSD, radius of gyration (rGyr), intra-ligand hydrogen bonds, molecular surface area (MolSA), solvent-accessible surface area (SASA), and polar surface area (PSA) were all monitored during the 100 ns molecular dynamics simulation to assess ligand dynamic characteristics. The RMSD of the ligand did not change significantly after the initial equilibration phase, suggesting that the ligand is still bound within the active site. No substantial changes were observed

in the compactness of the ligands in rGyr, which also showed minimal fluctuations during the simulation. MolSA and PSA were not significantly affected, and SASA was only transiently affected with no lasting changes of solvent exposure with limited intramolecular hydrogen bonding which demonstrate the structural integrity of the ligands is maintained.

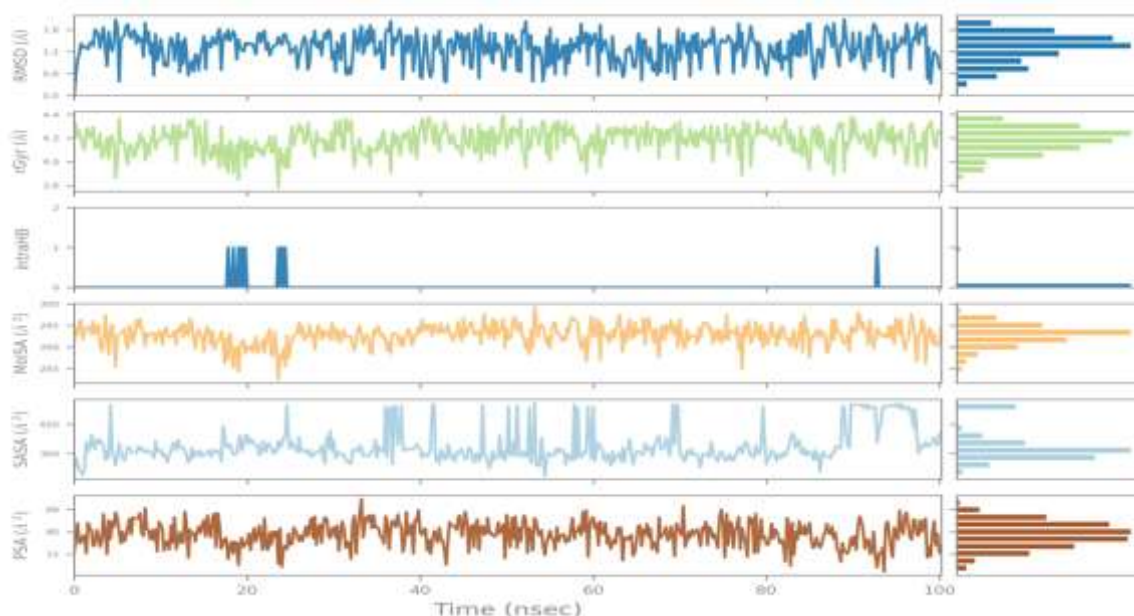


Figure 14. Time evolution of ligand properties including RMSD, radius of gyration (rGyr), intramolecular hydrogen bonds (intraHB), molecular surface area (MolSA), solvent-accessible surface area (SASA).

3.4. Binding Free Energy Calculation (MM/GBSA)

3.4.1. Binding Free Energy Analysis of 6UBS–Ligand Complexes (MM/GBSA)

The binding free energies of the docked complexes were further evaluated with MM/GBSA analysis (table 8). The calculated ΔG_{bind} values ranged between -15.56 to -40.53 kcal/mol which showed the different binding affinity of the selected phytoconstituents. The binding free energy was the best for rutin (CID: 5280805) with a value of $(-40.53$ kcal/mol), followed by tropine esters with a value of $(-38.41$ kcal/mol). Whereas linalool and citral showed moderate binding affinities. The energy decomposition analysis exhibited that the complex stabilisation is mainly due to van der Waals and lipophilic interactions. However, the results of MM/GBSA showed good consistency with the molecular docking results, confirming that rutin and tropine esters were the most favourable binders to the glycine receptor (6UBS).

Table 8. MM/GBSA binding free energy (ΔG_{bind}) and major energy components of selected phytoconstituents.

Molecule (CID)	ΔG_{bind} (kcal/mol)	vdW (kcal/mol)	Coulomb (kcal/mol)	Lipophilic (kcal/mol)	Solv_GB (kcal/mol)
5280805	-40.53	-34.01	-85.33	-16.08	95.52
3000322	-38.41	-24.36	-2.43	-16.65	6.84
643779	-27.69	-19.69	0.18	-12.96	4.13
638011	-23.95	-18.13	-0.49	-12.63	5.76
5280863	-17.38	-13.38	-121.66	-6.59	125.06
5280343	-15.56	-13.15	-120.67	-6.38	125.90

The MM/GBSA binding free energy and energy decomposition analysis of the selected compounds in complex with 6UBS are shown in Table 9. Linalool exhibited the best binding affinity with binding free energy of -33.11 kcal/mol. The energy

decomposition analysis revealed that linalool binding was more lipophilic in nature (-14.17 kcal/mol). The binding affinity of apigenin, however, was decreased due to its greater polar solvation energy (8.45 kcal/mol) compared to linalool (4.58 kcal/mol). Ligand strain energy was also lower for linalool (1.03 kcal/mol) than for apigenin (4.70 kcal/mol), indicating a more favourable bound conformation. However, the present data suggest different binding modes, linalool involving more hydrophobic interactions and apigenin more electrostatic interactions in the active site of 6UBS.

Table 9. MM/GBSA binding free energy (ΔG_{bind}) and key energy contributions of selected compounds.

Molecule (CID)	ΔG_{bind} (kcal/mol)	Coulomb (kcal/mol)	H-bond (kcal/mol)	Lipophilic (kcal/mol)	vdW (kcal/mol)	Solv_GB (kcal/mol)	Ligand Strain (kcal/mol)
5280443	-27.72	-11.92	-1.00	-6.55	-21.21	8.45	4.70
6549	-33.11	-4.40	-0.54	-14.17	-19.56	4.58	1.03

3.4.2. MM/GBSA Binding Free Energy Analysis of Phytoconstituents against 4COF.

The selected phytoconstituents MM/GBSA binding free energy and energy decomposition profiles are depicted in Table 10 in complex with 4COF (GABAA receptor). The binding free energy (ΔG_{bind}) of rutin is most favourable with the value of -39.04 kcal/mol. Based on the energy decomposition analysis results, electrostatic interactions were the most important factor in the binding of rutin, accounting for the highest energy contributions of the Coulomb (-80.93 kcal/mol) and hydrogen-bond (-3.46 kcal/mol) energies. However, rutin exhibited the highest ligand strain energy (12.29 kcal/mol), its favourable intermolecular interactions compensated for this conformational penalty, resulting in the lowest ΔG_{bind} .

Table 10. MM/GBSA binding free energy (ΔG_{bind}) and key energy contributions of selected phytoconstituents in complex with the 4COF protein.

Molecule (CID)	ΔG_{bind} (kcal/mol)	Coulomb (kcal/mol)	H-bond (kcal/mol)	Lipophilic (kcal/mol)	vdW (kcal/mol)	Solv_GB (kcal/mol)	Ligand Strain (kcal/mol)
5280805	-39.04	-80.93	-3.46	-13.34	-19.66	71.67	12.29
5280343	-27.34	-45.83	-2.01	-10.78	-19.79	55.44	-1.74
5280443	-27.72	-11.92	-1.00	-6.55	-21.21	8.45	4.70
643779	-24.49	-13.11	-0.53	-12.90	-17.44	17.29	1.63
638011	-24.84	-8.43	-0.55	-14.46	-19.53	17.09	1.71
5280863	-23.71	-43.20	-1.31	-11.91	-20.20	52.63	2.81
3000322	-23.31	-6.88	-1.10	-15.34	-22.24	22.70	4.67

Table 11. MM/GBSA binding free energy (ΔG_{bind}) and major energy contributions of selected compounds.

Molecule (CID)	ΔG_{bind} (kcal/mol)	Coulomb (kcal/mol)	H-bond (kcal/mol)	Lipophilic (kcal/mol)	vdW (kcal/mol)	Solv_GB (kcal/mol)	Ligand Strain (kcal/mol)
5280443	-28.60	-24.00	-1.45	-8.87	-17.12	25.61	1.48
6549	-10.54	-3.00	-0.59	-11.73	-18.23	21.94	2.44

The MM/GBSA binding free energy and energy decomposition profiles of apigenin and linalool in complex with 4COF receptor are shown in Table 11. Apigenin has a more favourable binding free energy $\Delta G_{\text{bind}} = -28.60$ kcal/mol suggesting that it has higher binding affinity to the 4COF receptor. The energy decomposition analysis indicated that the electrostatic contributions (Coulomb energy: -24.00 kcal/mol) to the binding of apigenin were much larger than those for linalool. In both complexes, van der Waals forces played a similar role, whereas polar solvation energy opposed binding in each case. However, apigenin had a lower ligand strain energy (1.48 kcal/mol), which shows a more favourable bound conformation. Hence, these findings demonstrate that electrostatic interactions are the key factor in the higher binding affinity of apigenin to the 4COF receptor.

3.5. Comparative and Synergistic Binding Analysis

Comparative MM/GBSA analysis of the 6UBS and 4COF targets shown distinct binding preferences among the selected phytoconstituents. Rutin exhibited the most favorable binding free energies toward both 6UBS ($\Delta G_{\text{bind}} = -40.53$ kcal/mol) and 4COF ($\Delta G_{\text{bind}} = -39.04$ kcal/mol), whereas linalool showed stronger binding to 6UBS ($\Delta G_{\text{bind}} = -33.11$ kcal/mol) than to 4COF ($\Delta G_{\text{bind}} = -10.54$ kcal/mol). In contrast, apigenin demonstrated comparable binding to both targets, with ΔG_{bind} values of -27.72 kcal/mol for 6UBS and -28.60 kcal/mol for 4COF. Energy decomposition analysis indicated that binding to 6UBS was predominantly driven by van der Waals and lipophilic interactions, whereas electrostatic interactions contributed more substantially to ligand stabilization in the 4COF binding pocket. These complementary interaction profiles suggest differential target engagement by phytoconstituents from *Cymbopogon citratus* Stapf and *Cassia auriculata* Linn, supporting the proposed synergistic multi-target modulation of epilepsy-associated proteins.

The present study integrated molecular docking and MM/GBSA analyses to investigate the multi-target binding potential of phytoconstituents from *Cymbopogon citratus* Stapf and *Cassia auriculata* Linn against the two targets involved in epilepsy namely 6UBS (Glycine receptor) and 4COF (GABAA receptor). The findings exhibited that different types of target-specific interaction mechanisms between the molecules, with van der Waals and lipophilic interactions are more important in the 6UBS binding pocket, while electrostatic interactions played a more significant role in the 4COF binding pocket. These differences reflect the effect of the structural and physicochemical properties of the target proteins on the binding properties of the ligands. Remarkably, rutin displayed the highest binding affinity to both targets, whereas linalool had a higher binding affinity to 6UBS and apigenin to both 6UBS and 4COF. Notably, rutin had the highest binding affinity to both targets, while linalool had higher binding affinity to 6UBS and apigenin to 6UBS and 4COF, indicating complementary binding to the selected phytoconstituents. The differential binding profiles suggest the proposed synergistic multi-target modulation approach, where structurally diverse phytoconstituents act on different molecular targets involved in epilepsy. While these computational results offer a mechanistic understanding of the possible anticonvulsant activity of the phytoconstituents, experimental testing of their pharmacological effectiveness and synergy should be carried out in vitro and in vivo to verify their pharmacological effect.

4. CONCLUSION

In the present study, an integrated computational approach was used to gain insight into the multi-target antiepileptic potential of phytoconstituents of *Cymbopogon citratus* Stapf and *Cassia auriculata* Linn. by performing molecular docking, MM/GBSA, molecular dynamics simulation and ADMET prediction. The binding affinities of the selected phytoconstituents were found to be favourable with 6UBS and 4COF targets associated with epilepsy, the stability of protein–ligand interaction were also found to be acceptable and the pharmacokinetic characteristics were also well accepted. The compounds evaluated exhibited that rutin has the highest binding affinity, linalool has favourable CNS-related pharmacokinetic properties and preferential binding to 6UBS, while apigenin have consistent binding affinity to both targets and is a potential multi-target modulator. Overall, the computational results validate the proposed synergistic multi-target therapeutic approach of these phytoconstituents against epilepsy as well as give a scientific basis for the further study of these compounds. However, experimental validation through *in vitro* and *in vivo* studies is required to confirm the predicted biological activity, synergistic effects, and therapeutic potential.

AUTHOR CONTRIBUTIONS

Pratiksha Prashant Jadhav : Conceptualization, Investigation, Methodology, Laboratory Analysis

Pratima Arun Tatke: Data Curation, Supervision, Writing-Review & Editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this study.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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