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Investigating the role of phytochemicals from *Euphorbia pulcherrima* and *Ricinus communis* in modulating estradiol 17-beta -dehydrogenase 1 activity for breast cancer treatment

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Cancer, characterized by uncontrollable cell proliferation, poses a significant global health challenge, with breast cancer being one of the most prevalent and lethal forms. Despite advancements in treatment, the rising prevalence and mortality rates underscore the need for innovative therapeutic approaches. This study focuses on the first enzyme of the HSD17B family, specifically the HSD17B1 enzyme, known for its role in estrogen production and its impact on the spread of breast cancer cells. Targeting this enzyme, particularly 17-beta-Hydroxysteroid dehydrogenase type 1 (17-beta-HSD1), presents a promising avenue for treatment. Utilizing molecular docking and molecular dynamics simulations, we investigated the binding potential of phytoconstituents from *Euphorbia pulcherrima* and *Ricinus communis* on the Estradiol 17-beta-Dehydrogenase 1 enzyme. The study focuses on compounds such as Rutin, Kaempferol-3-O-Glcoside, Stigmasterol, Beta-sitosterol, and Germanicol.Kaempferol-3-O-Glucoside and Stigmasterol also show potential, emphasizing the importance of specific interactions alongside docking scores. Molecular dynamics simulations reveal varying degrees of stability among the complexes, with Kaempferol-3-O-Glucoside demonstratingstable binding configuration, Stigmasterol showing higher flexibility, and Rutin displaying moderate structural fluctuations. This integrated approach provides a comprehensive understanding ligand-protein interactions, offering valuable insights for the design and optimization of potential therapeutic compounds targeting Estradiol 17-beta-Dehydrogenase in treatment of breast cancer.

Keywords: Breast cancer, Estradiol 17-beta-dehydrogenase, *Euphorbia pulcherrima*, *Ricinus communis*

Cancer is defined as uncontrolled and immortal growth of cells, representing a persistent abnormality in cellular behavior. This often leads to the invasion, metastasis, and aggressive spread of cancerous cells to various organs[1,2]. Among the prevalent malignancies, breast cancer (BC) stands out as one of the most common types. Specifically, it holds the second position in terms of cancer-related deaths in women, following lung cancer. In 2012, the documented cases of breast cancer reached 14 million, and projections suggest that by 2035, this number is expected to escalate to 24 million[3,4]. Reports indicate that at least one in every nine women will experience this disease during her lifetime[5,6]. Hormone dependency is a prevalent characteristic, with approximately 60% of premenopausal BC patients and 75% of postmenopausal BC patients demonstrating this hormonal reliance. This highlights the diverse nature of BC and the importance of considering age as a factor in understanding its incidence and characteristics[7-9]. Current cancer treatments, mainly surgery, radiation, and chemotherapy, often yield limited benefits with significant side effects. Research prioritizes finding naturally occurring, low-toxicity chemicals for more effective and tolerable therapies[10-12]. Despite advancements in cancer research and treatment, late-stage identification remains common. Early detection is crucial for reducing late-stage fatalities. Therefore, the search for safe and effective cancer treatments or medications is imperative[13].

Breast cancer is a complex disease influenced by various molecular factors, and understanding the role of specific enzymes is crucial for developing targeted therapies[14]. One such enzyme of significant interest is 17-beta-Hydroxysteroid dehydrogenase type 1 (17-beta-HSD1). This enzyme belongs to the HSD17B enzyme family and plays a pivotal role in the

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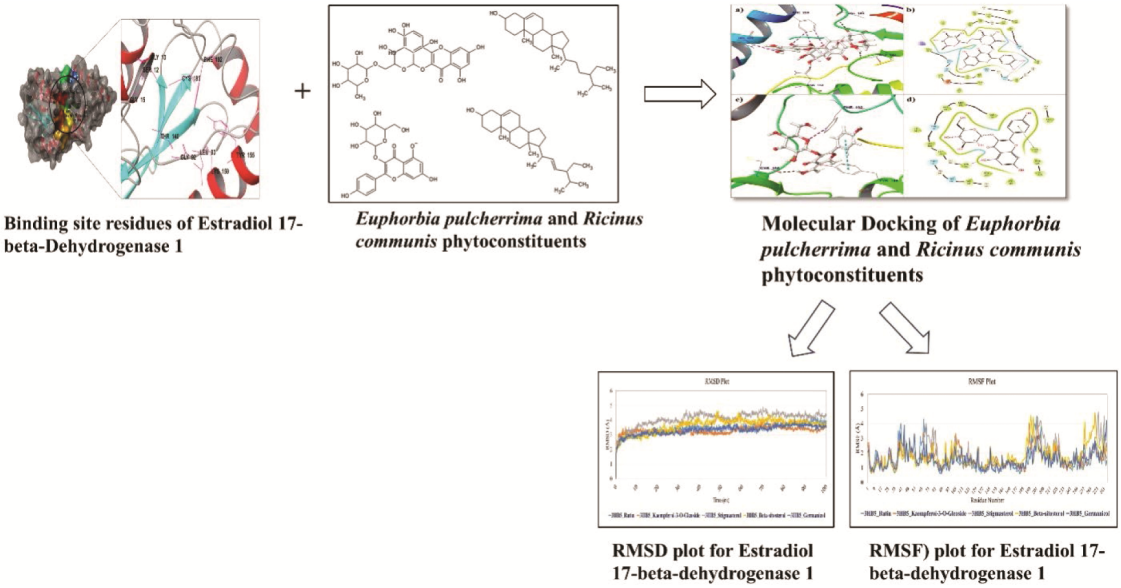

Graphical Abstract

conversion of 17beta-hydroxysteroids, including oestrogens and androgens[15,16]. In the context of breast cancer, the overexpression or hyperactivity of 17-beta-HSD1 has been linked to the accelerated spread of breast cancer cells through increased cell proliferation[17-20]. This suggests that targeting 17-beta-HSD1 could potentially be a promising avenue for breast cancer treatment.

Developing highly selective inhibitors of 17-beta-HSD1 could be a critical step in designing effective and safe therapeutic interventions. In contemporary medical research, phytochemicals have garnered significant attention due to their potential therapeutic applications. These natural compounds play a vital role in the development of various therapeutic drugs, showcasing a range of positive effects on human cancer models[21-24]. Phytochemicals are bioactive compounds derived from plants, possessing diverse pharmacological properties[25]. The study investigates the phytochemicals derived from *Euphorbia pulcherrima* and *Ricinus communis*, aiming to unravel their potential in combating cancer. *Euphorbia pulcherrima*, commonly known as poinsettia, and *Ricinus communis*, the castor plant, are two botanical species that have garnered attention in recent years for their potential medicinal value, particularly in the realm of cancer research[26,27]. While both plants are widely known for their ornamental and industrial uses, respectively, their phytochemical components have become the focus of scientific investigation due to their promising anti-cancer properties. Poinsettia contains various phytochemicals, including flavonoids, alkaloids, terpenoids, quercetin, and kaempferol, which have demonstrated anti-inflammatory and anti-cancer properties in preclinical studies. Research on poinsettia extracts has shown potential anti-cancer effects, including inhibition of cell proliferation, induction of apoptosis (programmed cell death), and suppression of angiogenesis (the formation of new blood vessels that support tumor growth)[28-30]. These activities make poinsettia an intriguing candidate for further exploration in cancer therapy.

Alongside, the castor plant is rich in phytochemicals, with its seeds containing ricin, a well-known toxic protein. However, castor oil, derived from the seeds, also contains beneficial components such as ricinoleic acid, flavonoids, and polyphenols, which exhibit anti-inflammatory and anti-cancer properties. Ricinoleic acid, the main component of castor oil, has been studied for its anti-cancer effects. It has shown potential in inhibiting the growth of various cancer cell lines, inducing apoptosis, and disrupting cancer cell migration and invasion. Additionally, other castor oil components contribute to its overall anti-cancer activity[31]. Both *Euphorbia pulcherrima* and *Ricinus communis* show promise in cancer research due to their rich phytochemical composition. While more studies are needed to fully unravel their potential in combating cancer, the current research suggests that these plants may contribute valuable compounds for the development of novel anti-cancer therapies. It is important to note that the use of plant-derived

compounds for medical purposes requires rigorous investigation to ensure safety and efficacy.

In this context, the present study adopts a combined computational approach, integrating molecular docking and molecular dynamics (MD) simulations, to analyze the interaction and binding potential of phytoconstituents from *Euphorbia pulcherrima* and *Ricinus communis* with Estradiol 17-beta-Dehydrogenase 1, with a focus on their anticancer properties. By targeting Estradiol 17-beta-Dehydrogenase 1, these phytoconstituents may offer a novel avenue for breast cancer treatment. The findings of this research could contribute to the growing body of knowledge on phytochemicals as potential anticancer agents and may have implications for the development of future therapeutics.

Materials and Methods

Protein structure retrieval and preparation

The x-ray crystal structure of Estradiol 17-beta-Dehydrogenase 1 enzymeis available in the RCSB PDB database (https://www.rcsb.org/) with PDB ID: 3HB5[32] at 2 Å resolution (Fig. 1). After downloading the structure in pdb file format, we have then performed *In silico* protein structure preparation using Protein Preparation Wizard[33] of Schrodinger software. The process included hydrogenation, adjustment of protonation states, side-chain sampling, and energy minimization. The prepared structure was then validated for quality, and the final output was saved for subsequent molecular docking and simulation analyses.

Ligand structure retrieval and preparation

The 2D structures of *Euphorbia pulcherrima* and *Ricinus communis* phytoconstituents, including Rutin, Kaempferol-3-O-Glcoside, Stigmasterol, Beta-sitosterol, and Germanicol were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). To convert these 2D structures into 3D structures, the OpenBabel program was employed[34]. Subsequently, the obtained 3D structures underwent energy minimization using the Maestro software, employing the OPLS-2005 force field[35]. This process aimed to achieve energetically minimized structures for further utilization in molecular docking studies.

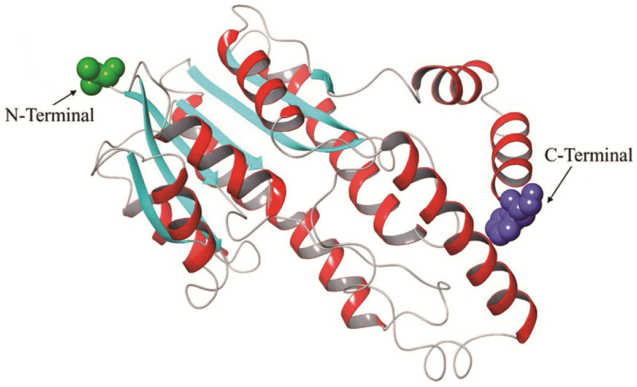

Fig. 1 — The 3D structure of the Estradiol 17-beta-Dehydrogenase 1 enzyme with PDB ID: 3HB5[32]. The helices shown in red colour, strands are shown in cyan colour and loops are shown in gray colour

Binding site definition and molecular docking study

The binding cavity of the Estradiol 17-beta-Dehydrogenase 1 enzyme is defined using FlexX software[36,37]. As, the crystal structure of 17-beta-Dehydrogenase 1 enzyme is available in complex with the inhibitor *i.e.*, 17beta-HSD type 1: a lead compound, so we have defined binding site by taking this compound as reference for binding site information using FlexX software. In FlexX when we prompt co-crystal ligand for reference ligand to define the binding site it automatically selects the binding site residue which are involved within the 6.5 position of the co-crystal ligand. For 17-beta-Dehydrogenase 1 enzyme we have selected amino acid residues viz. Ser12, Gly13, Gly15, Gly92, Lue93, Thr140, Tyr155, Lys159, Cys185, Val188, and Phe192 *etc* (Fig. 2).

After defining the binding site for Estradiol 17-beta-Dehydrogenase 1 enzyme, the prepared and energetically minimized ligand were subjected for molecular docking and binding affinity prediction using FlexX[36] and Hyde[38] software, respectively. After the docking and binding affinity prediction we have visualized the intermolecular interactions and subsequently performed the Molecular Dynamic (MD) simulation studies to see the binding stability of docked ligands within the binding cavity if the enzyme[39].

Molecular dynamic simulation

In this investigation, molecular dynamics simulations were conducted using the Desmond software[40] to explore the dynamic behavior of the complex system involving the Estradiol 17-beta-Dehydrogenase 1 enzyme and five phytoconstituents: Rutin, Kaempferol-3-O-Glcoside, Stigmasterol, Beta-sitosterol, and Germanicol. The simulations were executed under physiological conditions at 300K temperature, 1.01325 bar pressure, and within a cubic box of 10 Å. To accurately capture intermolecular interactions, the OPLS-2005 force field was employed, and solvation was achieved using TIP3P water molecules. The system underwent an initial energy

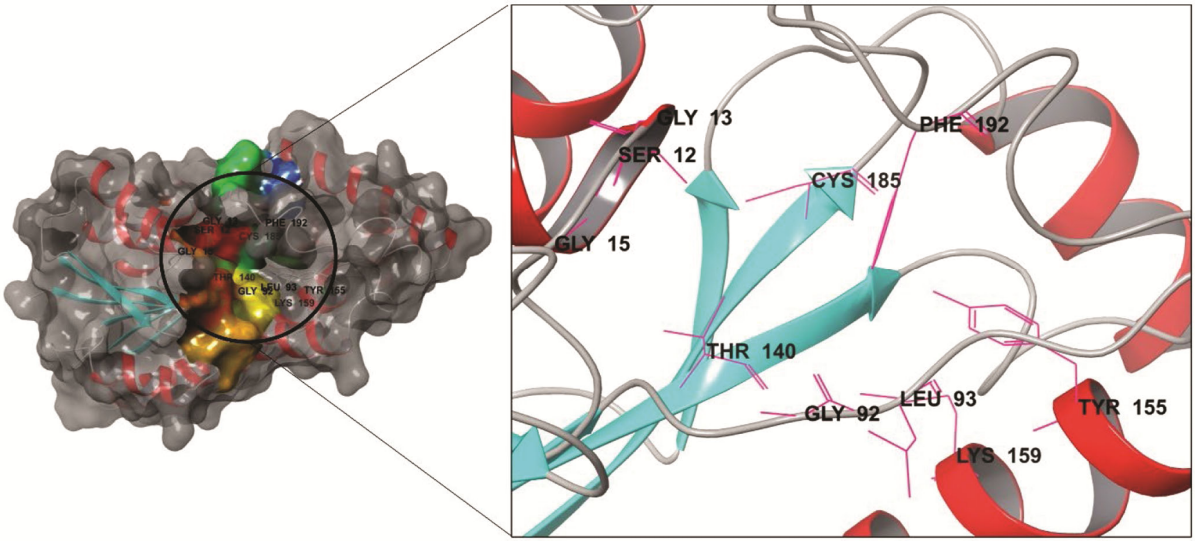

Fig. 2 — The selected binding site residues of Estradiol 17-beta-Dehydrogenase 1 enzyme for molecular docking calculations

Table 1 — Molecular interaction analysis of *Euphorbia pulcherrima* leaves and *Ricinus communis* seed phytoconstituents with Estradiol 17-beta-dehydrogenase 1 enzyme

Sr. No.	Name of the Compound	Docking Score (Kcal/mol)	Binding Affinity (Range in nm)	Interacting Residues	Interaction Type	Bond Distance (Å)
1	Rutin	-18.61	0	Ser142	HBond	1.34
				Asn152	HBond	1.12
				Val188	HBond	1.69
				His221		3.21
				Phe226	3 Ar-HBond	2.77, 3.42, 3.43
2	Kaempferol-3-O-Glcoside	-14.79	4771073.042 to 474034315.5	Cys185		2.01
				Tyr155	Pi-Pi Stacking	5.39
				Phe192	Ar-HBond	3.47
3	Stigmasterol	-8.21	21.984 to 2184.311	His221	Ar-HBond	3.05
4	Beta-sitosterol	-7.26	3.472 to 345.020	No Interactions		
5	Germanicol	-3.12	15785.265 to 1568359.421	No Interactions		

minimization to rectify steric clashes, followed by a gradual release of constraints for system relaxation. Equilibration stages (NVT and NPT) were implemented to adjust temperature and pressure through thermostats and barostats. Subsequently, production MD simulations were performed for 100 ns, with energy recorded at 1.2 ps intervals, and trajectories saved every 100 ps[41-43]. The simulations, conducted independently five times, aimed to scrutinize the stability and dynamics of the complex formed between the Estradiol 17-beta-Dehydrogenase 1 enzyme and the five phytoconstituents. Analysis of resulting trajectories utilized Desmond's tools, focusing on parameters such as RMSD and RMSF to offer insights into the system's behavior. This comprehensive approach contributes to a thorough understanding of the molecular dynamics exhibited by the studied complex.

Result and Discussion

Intermolecular interaction analysis

The molecular docking results provided in Table 1 gives valuable insights into the interactions between the Estradiol 17-beta-dehydrogenase 1 enzyme and different compounds, highlighting their potential as ligands. The compound, Rutin stands out with a robust docking score of -18.61 Kcal/mol, indicating a strong potential for binding. Notably, despite a binding affinity of 0 nm, suggesting steric clashes between the ligand and enzyme due to which binding affinity is not predicted by the software, Rutin establishes significant interactions (Fig. 3A & B). Hydrogen bonds with Ser142, Asn152, and Val188 at bond distances of with 1.34 Å, 1.12 Å, and 1.69 Å, respectively. It also involves in three aromatic hydrogen bonds with Phe226 at bond distances of 2.77 Å, 3.42 Å, 3.43 Å, showcase its ability to form

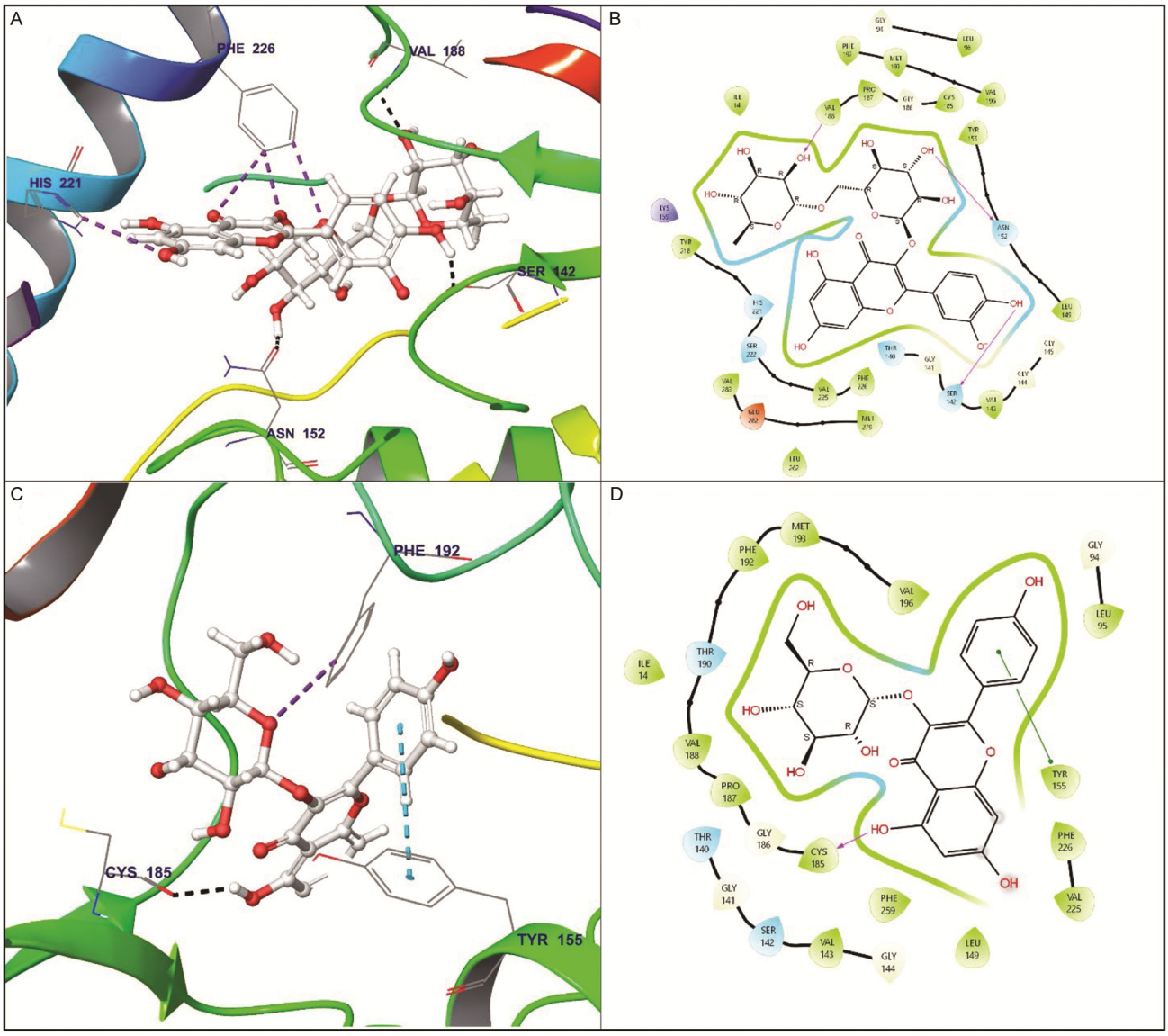

Fig. 3 — Intermolecular Interaction between *Euphorbia pulcherrima* and *Ricinus communis* seed phytoconstituents with Estradiol 17-beta-dehydrogenase 1 enzyme: (A) The 3D docked pose and interaction of Rutin with Enzyme; (B) The 2D interaction of Rutin with Enzyme; (C) The 3D docked pose and interaction of Kaempferol-3-O-Glcoside with Enzyme; and (D) The 2D interaction of Kaempferol-3-O-Glcoside with Enzyme. The enzyme structure is sown in ribbon form while the docked ligand shown in ball and stick model. The hydrogen bond, aromatic hydrogen bond and pi-pi stacking are shown in dashed black colored line, purple colored line, and cyan colored line respectively in 3D diagram. Whereas, in 2D diagram the hydrogen bonds are shown in pink colored line and pi-pi stacking are shown in green colored line by default by Maestro program. It was observed that the aromatic hydrogen bond interactions were not able to draw in the 2D diagram by software

stable interactions. These interactions suggest a favorable binding orientation despite the absence of measurable binding affinity.

In comparison, Kaempferol-3-O-Glucoside exhibits a slightly lower docking score of -14.79 Kcal/mol. Its binding affinity range (4771073.042 to 474034315.5 nm) indicates a potential variation in binding strength, with Pi-Pi stacking with Tyr155 at bond distance of 5.39 Å and an aromatic hydrogen bond with Phe192 (3.47 Å) contributing to its binding profile (Fig. 3C & D).

Stigmasterol, with a docking score of -8.21 Kcal/mol and a binding affinity range of 21.984 to 2184.311 nm, forms an aromatic hydrogen bond with His221 at bond distances of 3.05 Å (Fig. 4A & B). Although the docking score of Stigmasterol is lower than Rutin, the interaction with a key residue suggests a specific and potentially

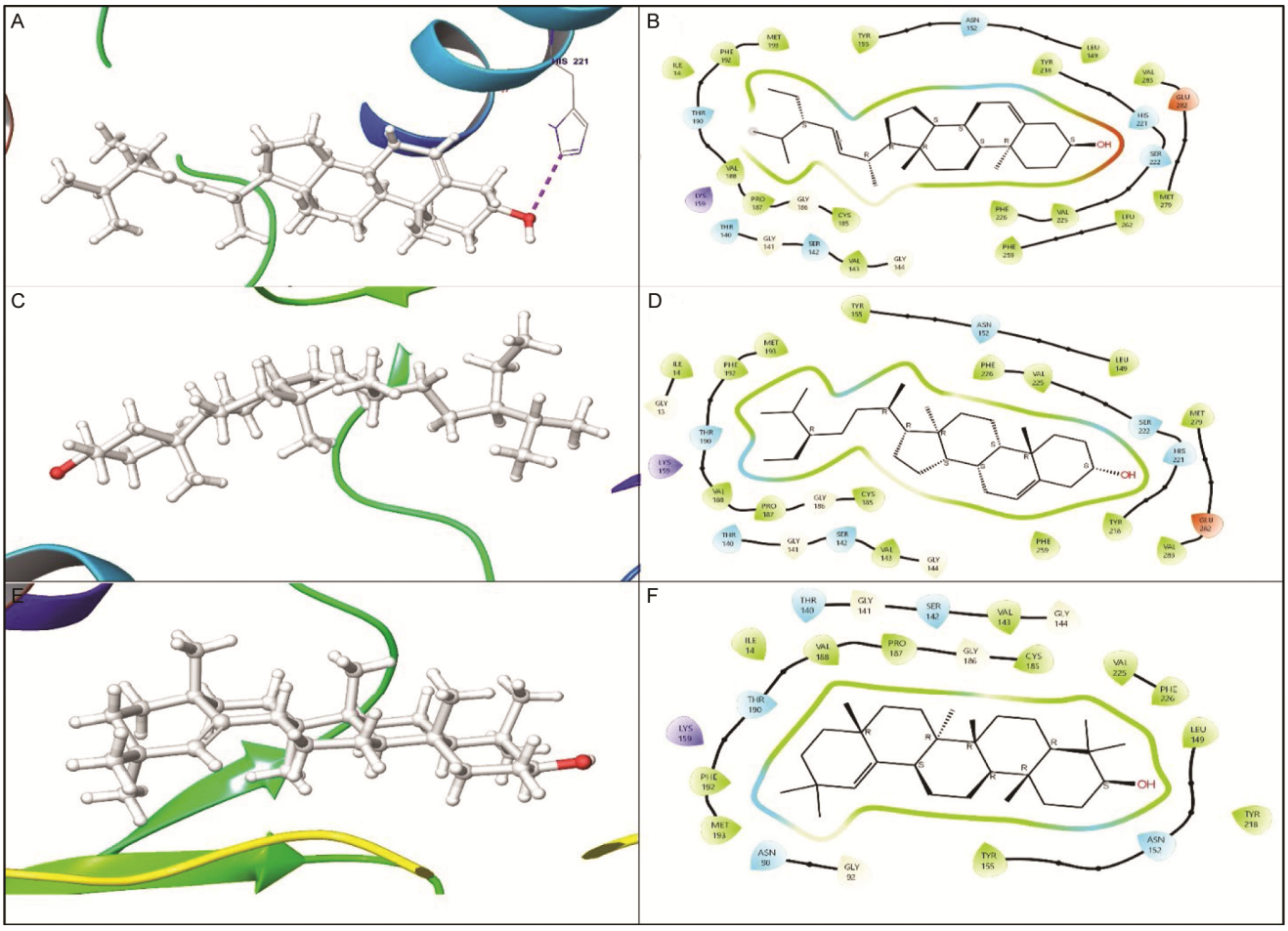

Fig. 4 — Intermolecular Interaction between *Euphorbia pulcherrima* leaves and *Ricinus communis* seed phytoconstituents with Estradiol 17-beta-dehydrogenase 1 enzyme: (A) The 3D docked pose and interaction of Stigmasterol with Enzyme; (B) The 2D interaction of Stigmasterol with Enzyme; (C) The 3D docked pose and interaction of Beta-sitosterol with Enzyme; (D) The 2D interaction of Beta-sitosterol with Enzyme; (E) The 3D docked pose and interaction of Germanicol with Enzyme; and (F) The 2D interaction of Germanicol with Enzyme. The enzyme structure is sown in ribbon form while the docked ligand shown in ball and stick model. The aromatic hydrogen bond shown in dashed purple colored line in 3D diagram. Whereas, in 2D diagram, it was observed that the aromatic hydrogen bond interactions were not able to draw in the 2D diagram by software

effective binding mode and it also shows the strong binding affinity.

On the other hand, Beta-sitosterol and Germanicol exhibit less favorable results. Beta-sitosterol's docking score is -7.26 Kcal/mol, with a binding affinity range of 3.472 to 345.020 nm, and no specific interactions mentioned (Fig. 4C & D). Germanicol, with a docking score of -3.12 Kcal/mol and a wide binding affinity range (15785.265 to 1568359.421 nm), also lacks specific interactions (Fig. 4E & F). These findings may indicate weaker binding affinities or steric clashes, limiting their potential as effective ligands.

In conclusion, Rutin emerges as a promising ligand despite the absence of measurable binding affinity, with strong specific interactions. Kaempferol-3-O-Glucoside and Stigmasterol also show potential, emphasizing the importance of considering both docking scores and specific interactions. Beta-sitosterol and Germanicol exhibit less favorable results, suggesting potential challenges in achieving effective binding.

Dynamic behavior of estradiol 17-beta-dehydrogenase 1 enzyme and ligand binding stability by MD simulation

From the MD simulation results, the RMSD values calculated from 1000 trajectories generated during 100 nanoseconds of MD simulations for different complexes involving the compounds Rutin, Kaempferol-3-O-Glucoside, Stigmasterol, Beta-sitosterol, and Germanicol with Estradiol 17-beta-dehydrogenase 1 enzyme (PDB ID: 3HB5) (Fig. 5A). The complex 3HB5_Rutin involving Rutin demonstrates an average

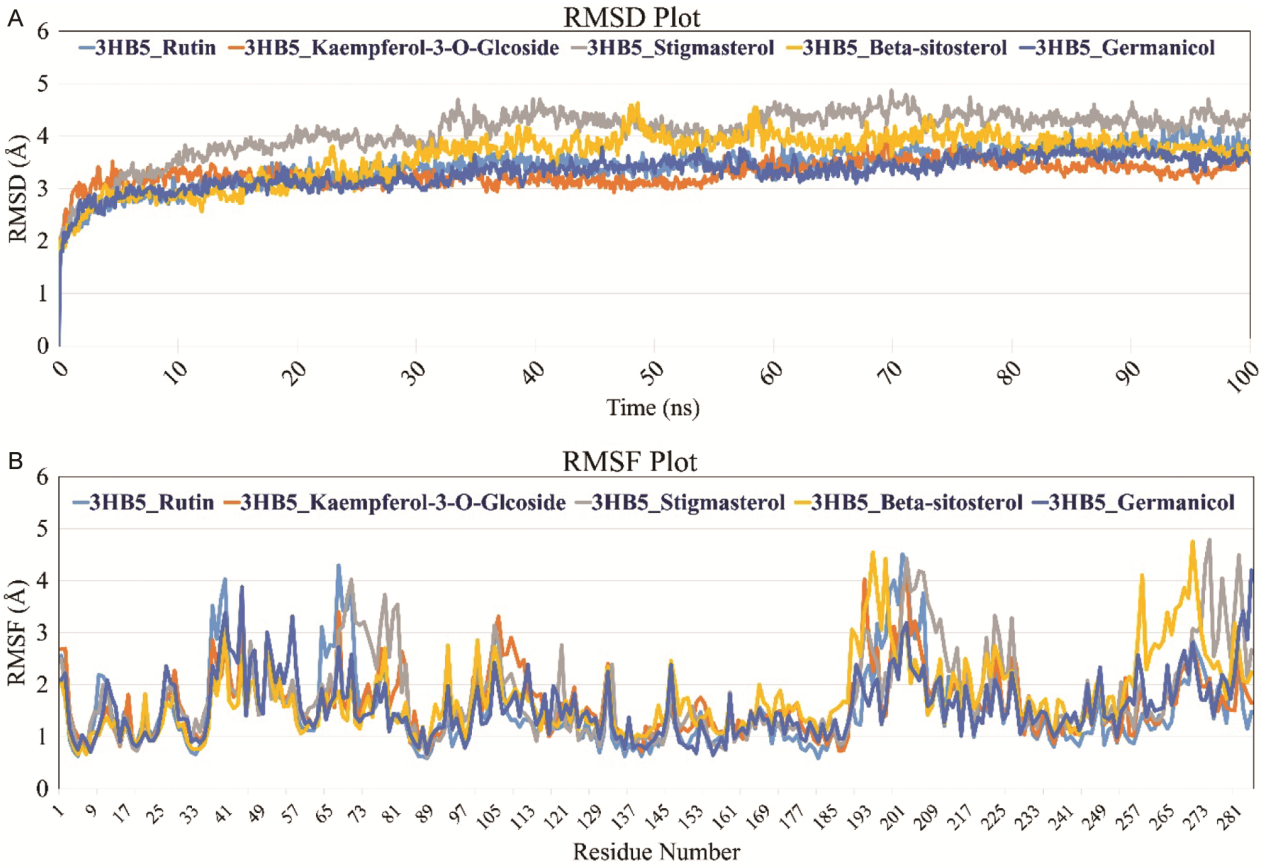

Fig. 5 — (A) Root Mean Square Deviation (RMSD); and (B) Root Mean Square Fluctuation (RMSF) plot for Estradiol 17-beta-dehydrogenase 1 enzyme when complexed with phytoconstituents during 100 ns of MD simulation time

RMSD of 3.43 Å with a standard deviation of 0.39 Å. This suggests a moderate level of structural fluctuation during the MD simulation. The lower standard deviation indicates relatively consistent behavior across the multiple trajectories, contributing to the overall stability of the complex.

The complex with Kaempferol-3-O-Glucoside exhibits a slightly lower average RMSD of 3.28 Å, with a comparatively lower standard deviation of 0.24 Å. These values collectively suggest that these complex experiences less structural deviation during the simulation, indicating a more stable binding configuration. In case of the Stigmasterol complex, it shows an average RMSD of 4.08 Å, the highest among the complexes in the table. The standard deviation of 0.48 Å suggests a notable degree of structural variability during the MD simulation. This higher RMSD may indicate that the Stigmasterol complex experiences more dynamic changes in its structure, potentially affecting its stability. For the Beta-sitosterol complex, the average RMSD is 3.61 Å, with a standard deviation of 0.48 Å. This suggests a moderate level of structural fluctuation, like the Rutin complex. The comparable standard deviation indicates a consistent behavior across trajectories, contributing to the overall stability of the complex. The Germanicol complex demonstrates an average RMSD of 3.31 Å with a standard deviation of 0.32 Å. These values indicate a moderate level of structural fluctuation during the MD simulation. The lower standard deviation suggests a more consistent behavior, contributing to the overall stability of the complex.

The RMSD values provide insights into the structural stability of the different complexes during the MD simulations. Kaempferol-3-O-Glucoside exhibits the lowest average RMSD and standard deviation, indicating a relatively stable binding configuration. Stigmasterol, on the other hand, shows the highest average RMSD, suggesting greater structural variability during the simulation. Rutin, Beta-sitosterol, and Germanicol complexes fall within a moderate range of structural fluctuation. These findings highlight the varying degrees of stability

among the complexes and can guide further investigations into the dynamics and structural changes of these ligand-protein interactions.

In evaluating the MD simulations alongside docking scores and binding affinities for the complexes involving Rutin, Kaempferol-3-O-Glucoside, Stigmasterol, Beta-sitosterol, and Germanicol, key findings emerge. The complex with Rutin exhibits a high docking score and specific interactions, yet its MD simulation reveals moderate structural fluctuations, possibly indicating ligand flexibility during binding. In contrast, Kaempferol-3-O-Glucoside shows a lower docking score but maintains a stable binding configuration with the lowest RMSD, suggesting robust ligand-receptor interactions. Stigmasterol demonstrates the highest RMSD, implying greater structural variability during MD simulations. Despite its lower docking score and a broad binding affinity range, the dynamic behavior observed raises questions about the stability of its binding conformation. Beta-sitosterol and Germanicol exhibit comparable stability during MD simulations, reflected in their moderate RMSD values. While their docking scores and binding affinities are also moderate, these compounds maintain a relatively consistent binding configuration, suggesting potential stability in their interactions.

Also, we have calculated the RMSF values for Estradiol 17-beta-dehydrogenase 1 enzyme when it binds with the phytoconstituents. The Figure 5B depict information on the RMSF calculated from 1000 trajectories generated during 100 nanoseconds of MD simulations for different complexes involving Rutin, Kaempferol-3-O-Glucoside, Stigmasterol, Beta-sitosterol, and Germanicol.

The complex with Rutin exhibits an average RMSF of 1.53 Å, with a standard deviation of 0.77 Å. These values suggest that the Rutin complex experiences moderate fluctuations in atomic positions during the MD simulations. The standard deviation indicates variability across trajectories, indicating certain regions may undergo more significant fluctuations. The Kaempferol-3-O-Glucoside complex shows a slightly higher average RMSF of 1.62 Å, with a standard deviation of 0.63 Å. Despite the slightly higher average RMSF, the lower standard deviation suggests more consistent atomic fluctuations across trajectories, indicating a relatively stable binding configuration. For the Stigmasterol complex, the average RMSF is 1.81 Å, with a standard deviation of 0.85 Å. These values suggest notable fluctuations in atomic positions during the MD simulations. The higher standard deviation indicates variability in the extent of fluctuations across different trajectories. The Beta-sitosterol complex demonstrates an average RMSF of 1.75 Å, with a standard deviation of 0.73 Å. Like Rutin, it experiences moderate fluctuations, with some variability across trajectories as indicated by the standard deviation. The Germanicol complex exhibits an average RMSF of 1.57 Å, with a standard deviation of 0.60 Å. These values suggest moderate atomic fluctuations during the MD simulations, with a relatively lower standard deviation, indicating more consistent behavior across trajectories.

Comparing the complexes, Kaempferol-3-O-Glucoside and Germanicol show slightly lower average RMSF values, indicating relatively stable binding configurations. Stigmasterol exhibits the highest average RMSF, suggesting more dynamic behavior during the simulations. Rutin and Beta-sitosterol fall within a moderate range of RMSF values. The RMSF values provide insights into the flexibility of different complexes during MD simulations. Kaempferol-3-O-Glucoside and Germanicol complexes demonstrate relatively stable binding configurations, while Stigmasterol exhibits higher flexibility. Rutin and Beta-sitosterol fall within a moderate range.

Conclusion

The interaction analysis identified the binding potential of phytoconstituents derived from *Euphorbia pulcherrima* and *Ricinus communis* with Estradiol 17-beta-dehydrogenase 1. Rutin hadpotential ligand properties with strong interactions, whereas, Kaempferol-3-O-Glucoside had stable and low RMSD, therefore possibly stabilizing it with this residue. Higher RMSD for stigmasterol indicates structural variability. The ligand remained stable and flexible as indicated by MD simulations and RMSF analyses and this will help design the therapy against this enzyme.

Conflict of interest

All authors declare no conflict of interest.

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