

Structure-Guided Discovery of 2-Phenylethanol as a Dual-Target Antifungal and Antiviral Agent: Integrative Docking, Dynamics, and ADMET Profiling Against Key Pathogenic Enzymes

Sahana T

Department of Plant Biotechnology, College of Agriculture, University of Agricultural Sciences, Bangalore (UAS-B), Bengaluru, India, 560065

Nagesha N

Department of Plant Biotechnology, College of Agriculture, University of Agricultural Sciences, Bangalore (UAS-B), Bengaluru, India, 560065

Naveen Hiremath

Organismic Technologies Pvt Ltd, Sai Orchard, Chikkabettahalli, Hesarghatta Main Road, Bengaluru, India, 560097

Dyumn Dwivedi

Centre for Multidisciplinary Research in Health Science (MACH), Università degli Studi di Milano Statale, Milano, Italy 201223

Chandralekha Nair

Centre for Multidisciplinary Research in Health Science (MACH), Università degli Studi di Milano Statale, Milano, Italy 201223

Uddalak Das

`uddalak_2025@jnu.ac.in`

Indian Council of Agricultural Research – National Institute of Plant Biotechnology (ICAR – NIPB), Indian Agricultural Research Institute (IARI), New Delhi, India 110012

Research Article

Keywords: 2-Phenylethanol, Temple tree, Broad-spectrum enzyme inhibition, Molecular dynamics simulation, Antifungal and antiviral phytocompounds

Posted Date: July 14th, 2025

DOI: <https://doi.org/10.21203/rs.3.rs-7098501/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: The authors declare no competing interests.

Abstract

The growing threat of multidrug-resistant fungal and viral pathogens underscores the urgent need for novel broad-spectrum therapeutics. In this study, we computationally evaluated the dual antimicrobial potential of 2-phenylethanol (2 PE), a phenyl-substituted aromatic alcohol derived from *Plumeria rubra*, against seven biologically essential targets using molecular docking, molecular dynamics (MD) simulations, and ADMET profiling. Docking studies revealed high binding affinities of 2 PE across fungal enzymes—*Candida albicans* N-myristoyltransferase, *Aspergillus niger* endoglucanase A, and *Penicillium chrysogenum* Sec3p–Rho1p—and viral enzymes—SARS-CoV-2 main protease, HIV-1 reverse transcriptase, HIV-1 protease, and hepatitis B virus capsid protein—with docking scores ranging from – 9.1 to – 14.4 kcal/mol. Key interactions included hydrogen bonding with catalytically critical residues such as His41, Cys145, Arg187, and Ser111. MD simulations over 100 ns confirmed structural stability of all complexes, with low RMSD (< 2.3 Å), consistent ligand positioning, stable radius of gyration, and persistent hydrogen bonding (> 80% occupancy). ADMET analysis indicated high intestinal absorption, low toxicity, non-mutagenicity, and minimal environmental risk, reinforcing the bioavailability and safety profile of 2 PE. The compound's favorable physicochemical properties, natural origin, and target-specific binding support its candidacy as a dual-action antiviral and antifungal agent. Although entirely *in silico*, these findings provide a mechanistic rationale for further *in vitro* and *in vivo* evaluation, including enzymatic inhibition assays, microbial growth studies, and structure–activity optimization. This study establishes 2 PE as a promising lead molecule for next-generation broad-spectrum antimicrobial development.

1. Introduction

Microbial infections remain a persistent and formidable challenge to global health, with viruses and fungi representing two particularly resilient classes of pathogens [1, 2]. While bacterial infections have seen major breakthroughs in treatment due to the advent and expansion of antibiotic therapies, the management of viral and fungal diseases continues to face substantial limitations [3, 4]. Viral pathogens, with their minimalistic structure and absolute dependence on host cellular machinery, are capable of causing a wide array of illnesses—from self-limiting conditions to chronic and life-threatening diseases [5]. Key to their replication and survival are essential viral enzymes such as proteases, which cleave large polyproteins into functionally active components critical for viral propagation [6]. In contrast, fungi, although historically less dominant as human pathogens, have emerged as significant clinical threats, especially among immunocompromised populations [7, 8]. The rising incidence of invasive fungal infections, coupled with the emergence of multidrug-resistant fungal strains, has further compounded the therapeutic challenge, exacerbated by a limited antifungal pharmacopeia and suboptimal clinical outcomes [9, 10].

The escalating problem of antimicrobial resistance, coupled with stagnation in the development of novel antiviral and antifungal drugs, has galvanized the scientific community to explore alternative therapeutic modalities [11, 12]. Among these, natural products derived from medicinal and aromatic plants (MAPs)

have garnered considerable attention due to their structural diversity and broad-spectrum bioactivity [13, 14]. One such plant, Frangipani or Temple tree (*Plumeria rubra*), has been traditionally valued for its pharmacological properties and is known to produce several volatile organic compounds (VOCs), including 2-phenylethanol (2 PE)—a phenyl-substituted aromatic alcohol widely used in the food, cosmetic, and fragrance industries [15, 16]. Beyond its commercial applications, 2 PE has recently emerged as a molecule of interest for its antimicrobial potential.

Evidence from phytopathogenic and clinical fungal models indicates that 2 PE exhibits potent antifungal activity through a multi-pronged mechanism. It has been shown to disrupt fungal protein synthesis by targeting aminoacyl-tRNA synthetases, particularly phenylalanyl-tRNA synthetase (PheRS), while also compromising mitochondrial function and destabilizing cell membranes [17]. Transcriptomic studies in fungi such as *Kloeckera apiculata* and *Saccharomyces boulardii* suggest that 2 PE interferes with aminoacyl-tRNA biosynthesis, oxidative stress regulation, and DNA replication [18]. Furthermore, 2 PE has been observed to impair the adhesion and biofilm formation of *Candida albicans*, thereby reducing its pathogenicity [19]. These findings position 2 PE as a promising antifungal agent with potential utility in clinical mycoses, particularly those refractory to current therapies.

Recent structural studies have expanded the landscape of potential antifungal targets beyond traditional enzymatic pathways. For instance, endoglucanase A (EglA) from *Aspergillus niger* plays a pivotal role in polysaccharide catabolism and fungal cell wall remodeling by hydrolyzing internal β -1,4-glucosidic linkages in cellulose and glucans [20]. Inhibition of EglA can weaken fungal cell wall integrity, rendering it an attractive target for antifungal development. Similarly, N-myristoyltransferase (NMT) from *Candida albicans* catalyzes the covalent attachment of myristate to substrate proteins—an essential post-translational modification for fungal growth and virulence. Blocking NMT activity disrupts protein localization and function, offering a validated strategy for antifungal intervention [21]. Another emerging target is Sec3p from *Saccharomyces cerevisiae*, in complex with the small GTPase Rho1p, which forms part of the exocyst complex regulating vesicle trafficking, cell wall biosynthesis, and cell polarity. Inhibiting the Sec3p-Rho1p interaction can compromise membrane trafficking and structural integrity of fungal cells, further broadening the scope of druggable targets in antifungal therapy [22, 23].

Despite the compelling antifungal evidence, the antiviral potential of 2 PE remains largely underexplored. Given its small molecular size, lipophilic character, and phenolic structure, it is plausible that 2 PE could engage in hydrophobic interactions with conserved active sites of key viral enzymes. One particularly attractive antiviral target is the main protease (M^{pro}) of SARS-CoV-2, which is indispensable for processing viral polyproteins into nonstructural proteins required for replication. Owing to its conserved catalytic dyad and well-characterized binding pockets, SARS-CoV-2 M^{pro} has become a focal point for antiviral drug discovery, with more than 550 crystallographic structures facilitating structure-based screening and rational inhibitor design [24, 25].

In this context, the dual antifungal and putative antiviral properties of 2 PE render it a promising candidate for further investigation. Computational methodologies—particularly molecular docking and

molecular dynamics (MD) simulations—offer a rapid and cost-effective strategy to predict and analyze molecular interactions between small ligands and macromolecular targets [26]. These *in silico* approaches have been instrumental in accelerating early-phase drug discovery, especially during emergent viral outbreaks such as COVID-19.

In this study, we present a comprehensive computational analysis of 2-phenylethanol against four biologically essential protein targets: (i) SARS-CoV-2 main protease (M^{pro}), crucial for viral replication; (ii) *Aspergillus niger* endoglucanase A (EglA), vital for fungal cell wall degradation; (iii) *Candida albicans* N-myristoyltransferase (NMT), indispensable for post-translational protein modification; and (iv) *Saccharomyces cerevisiae* Sec3p-Rho1p complex, a central regulator of vesicle trafficking and cell polarity. Through molecular docking and dynamic simulations, this study aims to evaluate the binding affinity, stability, and interaction profiles of 2 PE with these targets, thereby providing mechanistic insights into its antimicrobial action. By bridging the known antifungal activity of 2 PE with its hypothesized antiviral efficacy, our work lays the computational foundation for the development of 2 PE as a novel, dual-action antimicrobial agent suitable for addressing the pressing need for broad-spectrum therapeutics in the era of rising resistance.

2. Materials and Methods

2.1. Source and Preparation of Target Proteins

The target protein structures for both antiviral and antifungal analyses were retrieved from the RCSB Protein Data Bank (PDB) based on their relevance to viral replication and fungal viability. For the antiviral study, four viral proteins were selected: the chymotrypsin-like main protease (M^{pro}) of SARS-CoV-2 (PDB ID: 6LU7) [27], hepatitis B virus capsid protein (PDB ID: 3MSH) [28], HIV-1 protease (PDB ID: 3NU3) [29], and HIV-1 reverse transcriptase (PDB ID: 3LP1) [30]. For antifungal evaluation, three fungal protein structures were selected: *Aspergillus niger* phenylalanyl-tRNA synthetase (PDB ID: 1KS5) [31], *Candida albicans* N-myristoyltransferase (PDB ID: 1NMT) [32], and a mitochondrial protein from *Penicillium chrysogenum* (PDB ID: 3A58) [33]. All protein structures were prepared for docking using the Dock Prep tool in UCSF Chimera v1.16 [34]. This preprocessing step included the addition of hydrogen atoms, removal of water molecules and co-crystallized ligands, and assignment of partial atomic charges using the AMBER99 force field [35]. Non-protein molecules such as DNA, dNTPs, and metal ions—if present—were manually removed to avoid interference in docking.

2.2. Ligand Retrieval and Preparation

The primary test compound, 2-phenylethanol (CID: 6054), was selected based on its known antifungal potential and hypothesized antiviral activity. Its 3D structure was generated using MarvinSketch from the ChemAxon suite. Comparative standard drugs for antiviral docking included Darunavir (CID: 213039), Zidovudine (CID: 35370), and Lamivudine (CID: 60825), while Fluconazole (CID: 3365) and Voriconazole (CID: 71616) were used as reference antifungals. All chemical structures were obtained from the PubChem database in SDF format and converted to MOL2 format using Open Babel GUI [36]. Ligands

were geometry optimized and assigned appropriate partial charges to ensure compatibility with the docking protocol.

2.3. Active Site Prediction

The active site residues of the target protein were identified using the Computed Atlas of Surface Topography of proteins (CASTp) server [37], which analyzes pocket and cavity geometry (**Supplementary Table S1** and **Supplementary Table S2**). The amino acid residues delineating the predicted binding pocket were subsequently used to define the docking grid. Molecular docking was then performed with the grid box centered on this predicted active site.

2.4. Molecular Docking Analysis

Automated molecular docking simulations were carried out using the SwissDock web server (<http://www.swissdock.ch/>) [38], which utilizes the EADock DSS engine. The docking protocol was set to the “Accurate” parameter level to maximize the number of sampled binding modes and enhance prediction precision. Both ligand and protein structures were uploaded in PDB or MOL2 formats, as appropriate. Each docking run yielded multiple binding clusters ranked according to their FullFitness (FF) scores, where more negative values reflect stronger and more favorable binding interactions. The best-docked poses (i.e., cluster 0 or those with the most favorable FF scores) were selected for visualization and interpretation. UCSF Chimera v1.16 was used to generate all molecular interaction figures in 3D, while PyMOL v3.0.5 and BIOVIA Discovery Studio Visualizer v24.1.0.23298 were used for additional 3D and 2D interaction mapping, respectively.

2.5. In silico ADME/T and Toxicity Analysis

To assess the drug-likeness and pharmacokinetic behavior of 2-phenylethanol and other compounds, comprehensive ADMET profiling was performed using multiple *in silico* tools. These included Schrödinger’s QikProp module, SwissADME [39], ProTox-3.0 [40], ADMETlab 3.0 [41], and pkCSM [42]. Parameters such as gastrointestinal absorption, blood–brain barrier permeability, cytochrome P450 interactions, hepatotoxicity, carcinogenicity, mutagenicity, and other toxicity risks were evaluated. Additionally, drug-likeness criteria such as Lipinski’s Rule of Five, Veber, Ghose, and Egan filters were analyzed to determine the medicinal chemistry friendliness and oral bioavailability of the tested compounds.

2.6. Molecular Dynamics Simulation and Trajectory Analysis

The most promising protein–ligand complexes from docking studies were subjected to molecular dynamics (MD) simulations using GROMACS 2024.2 [43], employing the CHARMM36 [44] all-atom force field. Ligand topologies were generated using the CGenFF server. Each protein–ligand system was solvated in a triclinic box filled with TIP3P [45–47] water molecules and neutralized by adding Na⁺ or Cl[−] counterions. Energy minimization was conducted using the steepest descent algorithm for 20,000 steps. Equilibration was performed under the NVT and NPT ensembles for 100 ps each, using the Nosé–

Hoover thermostat and Parrinello–Rahman barostat, respectively. Production MD simulations were run for 100 ns.

Post-simulation analyses included calculation of root mean square deviation (RMSD) to monitor structural stability, root mean square fluctuation (RMSF) to assess residue flexibility, radius of gyration (Rg) to evaluate protein compactness, hydrogen bond dynamics, and solvent-accessible surface area (SASA) to probe solvation effects. Additionally, principal component analysis (PCA) was conducted to explore the dominant motions of protein-ligand complexes, and the free energy landscape (FEL) was derived using the formula $F(X) = kBT \ln P(X)$, where $P(X)$ denotes the conformational probability. Data visualization was performed using Matplotlib (Python), XMGrace, and VMD [48] for trajectory rendering.

3. Results

3.1. Docking Analysis Against Fungal Targets

Molecular docking studies revealed that 2-phenylethanol (2-PE) demonstrated superior binding affinity toward all selected fungal protein targets compared with clinically approved antifungal agents, Fluconazole and Voriconazole (Table 1). Against *Candida albicans* N-myristoyltransferase (PDB ID: 1NMT), 2-PE showed the highest docking score of – 11.6 kcal/mol, significantly outperforming Fluconazole (–9.4 kcal/mol) and Voriconazole (–9.5 kcal/mol). It formed multiple hydrogen bonds with active-site residues such as ARG187, ASN204, and ASN421 (distances ranging from 2.06 to 2.72 Å), along with extensive hydrophobic interactions involving residues like ILE215, LYS434, and TYR283. Additional binding mode analysis revealed hydrogen bonds with ASN54, GLN207, and LYS85, as well as π -interactions with PRO82 and TYR30, suggesting a deep and stable accommodation of 2-PE in the active site, likely due to favorable topology and residue orientation. In the case of *Penicillium chrysogenum* (PDB ID: 3A58), 2-PE achieved a docking score of – 9.2 kcal/mol, better than Fluconazole (–8.7 kcal/mol) and Voriconazole (–8.9 kcal/mol), engaging in hydrogen bonding with ARG73, ASN201, ASN119, LYS179, and SER125, in addition to π - π stacking with PHE120 and π -alkyl interactions with LEU131, PHE44, and PRO121. For *Aspergillus niger* (PDB ID: 1KS5), 2-PE exhibited a docking score of – 9.1 kcal/mol, again surpassing the controls. Key interactions included hydrogen bonding with ASP99 and SER111 (as low as 2.002 Å), and additional contacts with ASN99, ASN101, and ASN103, plus π -alkyl stabilization with TRP227 (Fig. 1 and Table 2).

Table 1
Comparative Docking Scores of 2-Phenylethanol and Standard Antifungal Drugs
Against Key Fungal Protein Targets

Ligands	<i>Aspergillus niger</i> (PDB:1KS5)	<i>Candida albicans</i> (PDB:1NMT)	<i>Pencillium chrysogenum</i> (PDB:3A58)
2-PE	-9.1	-11.6	-9.2
Fluconazole	-8.8	-9.4	-8.7
Voriconazole	-8.7	-9.5	-8.9

Table 2

Docking scores and non-covalent interaction profile of 2-phenylethanol with fungal and viral protein targets, including hydrogen bonding and hydrophobic contacts.

Target	Organism	Docking score (kcal/mol)	H-Bond Interactions (Å)			Hydrophobic Interactions
			Donor	Acceptor	Distance	Residue/Type
1KS5	<i>Aspergillus niger</i>	-9.1	GLN200:HE22	2-PE:O1	2.002 Å	TRP22 (3.852 Å, Pi–Pi Stacked), TRP22 (3.857 Å, Pi–Pi Stacked)
			2-PE: H10	ASP99:OD1	2.021 Å	
			2-PE: H4	SER111:O	2.933 Å (C-H bond)	
1NMT	<i>Candida albicans</i>	-11.6	ARG187:HH22	GLN203:OE1	2.72 Å	ILE215 (5.41 Å, Alkyl), PRO217 (4.89 Å, Alkyl), LYS434 (3.95 Å, Alkyl), PRO78 (5.27 Å, Alkyl), ARG187 (5.46 Å, Alkyl), PRO217 (4.65 Å, Alkyl), TYR283 (4.47 Å, Pi–Alkyl), TYR283 (4.88 Å, Pi–Alkyl), 2-PE – PRO62 (5.35 Å, Pi–Alkyl), 2-PE – LEU66 (5.13 Å, Pi–Alkyl)
			ARG423:HH22	SER171:O	2.26 Å	
			ASN204:HD22	VAL158:O	2.43 Å	
			ILE215:H	ASN166:OD1	2.51 Å	
			ASN421:HD22	PRO78:O	2.06 Å	
			: 2-PE:H10	GLU297:OE2	2.08 Å	
			LYS65:HZ2	:2-PE:O1	2.15 Å	
			ARG187:HH22	ASP64:O	2.16 Å	
				GLU60:O	2.35 Å	
				THR159:OG1		
3A58	<i>Penicillium chrysogenum</i>	-9.2	ARG84:HH22	TYR39:O	2.86 Å	LEU131 (5.15 Å, Alkyl), LYS100 (4.61 Å, Alkyl), ILE115 (5.33 Å, Alkyl), LEU131 (5.03 Å, Alkyl), LYS136 (5.23 Å, Alkyl), ILE115 (5.28 Å, Alkyl), LEU131 – TYR/PHE44 (4.48 Å, Pi–Alkyl), LYS134 –
			LYS136:HZ3	PHE44:O	2.13 Å	
			ARG73:HH22	ASN201:O	2.71 Å	
			ARG73:HH21	ASN201:O	2.54 Å	
			ARG11:HH12	THR101:O	2.82 Å	
			ARG11:HH12	GLY102:O	2.66 Å	
			: 2-PE:H10	LYS119:O	2.03 Å	
			: 2-PE:H3	LYS119:O	2.83 Å	
			ARG73:HH12	THR200:O	3.02 Å	

Target	Organism	Docking score (kcal/mol)	H-Bond Interactions (Å)			Hydrophobic Interactions
			Donor	Acceptor	Distance	Residue/Type
			ARG73:HH22	THR200:O	2.43 Å	PHE44 (5.39 Å, Pi-Alkyl), LYS136 – PHE44 (4.61 Å, Pi-Alkyl), TRP63 – LEU131 (5.48 Å, Pi-Alkyl), PHE77 – PRO41 (5.32 Å, Pi-Alkyl), 2-PE – PRO121 (5.40 Å, Pi-Alkyl)
			ARG73:HH22	ASN201:O	2.41 Å	
			LYS136:HE2	GLU45:OE1	2.82 Å	
6LU7	SARS-CoV-2	-10.2	:2-PE:H10	A: GLN189:OE1	2.103 Å	A: MET49 (4.685 Å, Pi-Alkyl)
			:2-PE:H10	A: GLN189:OE1	2.103 Å	
3MSH	Hepatitis-B	-9.7	:2-PE:H10	A:MET75:O	2.095 Å	A: VAL84 (4.007 Å, Pi-Alkyl)
			:2-PE:H10	A:MET75:O	2.095 Å	
3NU3	HIV-1 protease	-11.8	ARG8:HH11	ASP129:OD2	1.965 Å	HIS69 – PHE199 (3.771 Å, Pi-Pi T-shaped), ILE3 – LEU197 (5.378 Å, Alkyl), PHE99 – PRO101 (4.252 Å, Pi-Alkyl), PHE99 – ILE193 (5.273 Å, Pi-Alkyl), 2-PE – ALA128 (3.938 Å, Pi-Alkyl)
			GLN2:HE21	ASN198:OD1	1.872 Å	
			ILE3:H	LEU197:O	1.755 Å	
			ARG8:HE	ASP129:OD1	1.887 Å	
			THR26:H	THR126:OG1	1.949 Å	
3LP1	HIV-1 reverse transcriptase	-14.4	GLN85:HE22	GLU53:O	1.94 Å	TRP410 (3.732 Å, Pi-Pi T-shaped), TRP535 (4.67 Å, Pi-Alkyl), ALA408 (4.69 Å, Alkyl), PRO433 (5.30 Å, Alkyl), ILE542 (5.13 Å,
			TRP88:H	PRO52:O	1.95 Å	
			HIS96:H	ASN136:OD1	2.09 Å	
			TRP402:HE1	ASP364:OD1	2.26 Å	
			ALA408:H	PRO392:O	1.86 Å	
			TYR441:HH	LYS287:O	1.90 Å	

Target	Organism	Docking score (kcal/mol)	H-Bond Interactions (Å)			Hydrophobic Interactions
			Donor	Acceptor	Distance	Residue/Type
			GLY543:H	LEU283:O	1.95 Å	Alkyl), TRP88 (5.40 Å, Pi-Alkyl),
			ASN255:HD22	TYR532:OH	2.03 Å	TRP401 (4.95 Å, Pi-Alkyl),
			TRP401:HE1	GLN373:OE1	2.45 Å	TRP535 (4.70 Å, Pi-Alkyl),
			TRP401:HE1	TRP410:O	2.55 Å	VAL381 (5.15 Å, Alkyl), PRO52 (4.79 Å, Alkyl)

3.2. Docking Analysis Against Viral Targets

Docking analysis of 2-PE against viral protein targets revealed robust binding affinities that exceeded those of standard antiviral drugs such as Darunavir, Zidovudine, and Lamivudine (Table 3). The strongest interaction was observed with HIV-1 reverse transcriptase (PDB ID: 3LP1), where 2-PE exhibited an exceptionally high docking score of -14.4 kcal/mol, markedly better than Lamivudine (-9.6 kcal/mol), Zidovudine (-9.2 kcal/mol), and Darunavir (-10.7 kcal/mol). Multiple hydrogen bonds (1.86 – 2.55 Å) were formed with GLU53, TYR441, and TRP401, supported by π -alkyl and T-shaped π - π interactions. Against HIV-1 protease (PDB ID: 3NU3), 2-PE scored -11.8 kcal/mol, surpassing all controls, with hydrogen bonding to ASP129 and ASN198, π - π contacts with PHE199, and additional stabilization via ASP153, ILE150, and ILE164. In the SARS-CoV-2 main protease (PDB ID: 6LU7), 2-PE showed a docking score of -10.2 kcal/mol, forming dual hydrogen bonds with GLN189 and engaging MET49 through π -alkyl interactions, while also forming carbon-hydrogen bonds with HIS41, CYS145, and ARG188, contributing to a well-oriented binding pose. For the hepatitis B virus capsid protein (PDB ID: 3MSH), 2-PE demonstrated a docking score of -9.7 kcal/mol, forming stable hydrogen bonds with MET75 and GLN77, along with strong π - π stacking with HIS178 (~ 3.2 Å) and π -alkyl interactions with VAL84, ALA85, and ILE76. Additionally, in the HIV-1 integrase (PDB ID: 3LPI), 2-PE bound through hydrogen bonds with GLN161, MET164, and GLN143, complemented by π -interactions with VAL60 and TYR181 (Table 2 and Fig. 2).

Table 3
Comparative Docking Scores of 2-Phenylethanol and Standard Antifungal Drugs Against Key Viral Protein Targets

Ligand	SARS CoV-2 (PDB: 6LU7)	Hepatitis B (3MSH)	HIV-1 Protease (3NU3)	HIV-1 Reverse Transcriptase (PDB: 3LP1)
2-PE	-10.2	-9.7	-11.8	-14.4
Darunavir	8.1	-6.9	-7.5	-10.7
Zidovudine	-7.5	-6.6	-6.8	-9.2
Lamivudine	-7.9	-6.7	-7.0	-9.6

4. Pharmacokinetic and Toxicological Evaluation of 2-Phenylethanol for Agricultural Application

The ADMET and toxicity profile of 2-phenylethanol (2PE) underscores its strong potential as a safe, selective, and environmentally compatible antifungal and antiviral agent for agricultural use. Its low molecular weight (122.167 Da), moderate lipophilicity ($\log P = 1.22$), and limited number of hydrogen bond donors (1) and acceptors (1) enable optimal diffusion across microbial cell membranes and plant cuticles, supporting its systemic activity in plant tissues and rhizospheres. High predicted permeability (Caco-2 = 1.605 nm/s) and excellent intestinal absorption equivalent (88.07%) suggest strong bioavailability not only in plant models but also in phytopathogens upon foliar or root application. The low water solubility ($\log S = -1.198$) and low skin permeability ($\log K_p = -1.83$) imply a compound that is moderately hydrophobic, capable of adhering to plant surfaces and resisting rapid wash-off, making it suitable for field deployment. From an environmental toxicology standpoint, 2PE poses minimal aquatic risk, with low *Tetrahymena pyriformis* and minnow toxicity ($-0.385 \mu\text{g/L}$ and $2.048 \log \text{mM}$, respectively), indicating safety for aquatic ecosystems upon agricultural runoff. The compound is not a substrate or inhibitor of key efflux pumps or transporter analogues (e.g., P-gp), which are functionally conserved across microbial and plant systems, reducing the likelihood of resistance development through active extrusion in target pathogens. Crucially, 2PE does not interfere with xenobiotic-degrading enzyme systems analogous to cytochrome P450s in plants or fungi (except weak CYP1A2 inhibition), minimizing phytotoxicity and ensuring selectivity for pathogen enzymes. Its lack of hepatotoxicity, genotoxicity (non-AMES), and cardiotoxicity (non-hERG inhibitor) further supports environmental safety and non-target organism compatibility. The moderate clearance ($\log 0.325 \text{ ml/min/kg}$) and partial plasma unbound fraction (0.434) translate agriculturally to a balance between persistence in treated crops and biodegradability in soil matrices. Notably, 2PE's structural features—aromaticity, minimal rotatable bonds, and a phenolic hydroxyl group—enable strong and specific binding to microbial enzymes (as shown in docking), while retaining metabolic stability. These characteristics, combined with a low likelihood of bioaccumulation and negligible interaction with soil microbial detoxification pathways,

establish 2PE as a highly promising candidate for inclusion in next-generation agrochemicals, with potent dual antiviral and antifungal activity, high environmental safety, and minimal risk of resistance development (Fig. 3).

5. Atomistic Simulation Insights into 2Phenylethanol Binding with Fungal and Viral Pathogen Proteins

To thoroughly assess the dynamic behavior, structural stability, and binding interactions of 2phenylethanol (2PE) with fungal and viral targets, 100-nanosecond all-atom MD simulations were performed for each protein–ligand complex. Analyses included backbone and ligand RMSD, residue-specific RMSF, hydrogen bond occupancy, radius of gyration (Rg), and solvent-accessible surface area (SASA) to capture detailed conformational trends throughout the trajectories.

5.1. Antifungal Targets

5.1.1. *Aspergillus niger*

The RMSD of the 1KS5 backbone showed early convergence (~ 10 – 12 ns) to $\sim 2.2 \pm 0.2$ Å, evidencing overall structural stability of the enzyme in complex with 2PE. Ligand RMSD remained within 1.5–2.4 Å, with no increase indicative of detachment, confirming that 2PE remained snugly bound within the active site. Residue-level RMSF values remained below 1.5 Å for the majority of the protein; notably, Asn99, Leu120, Val121, Asn101, and Ser111—critical binding pocket residues—maintained even lower fluctuations (< 1.3 Å). Hydrogen bond analysis revealed that during over 80% of the simulation, at least one hydrogen bond was maintained, primarily with Asn99 and Ser111. Rg remained constant at 19.6 ± 0.2 Å, indicating stable protein compactness without significant unfolding. SASA values stabilized between 135 and 160 Å² following ~ 15 ns, reflecting burial of hydrophobic surfaces and persistent interaction of the ligand with the protein interior (Fig. 4).

5.1.2. *Candida albicans*

This complex equilibrated its backbone RMSD to $\sim 2.1 \pm 0.2$ Å by 10–15 ns and showed no major fluctuations for the remainder of the run. The ligand RMSD ranged narrowly between 0.6 and 1.8 Å, consistent with tight ligand binding. RMSF analysis confirmed that residues implicated in binding—Lys85, Gln207, and Pro82—remained highly stable with RMSF < 1.2 Å: overall mean fluctuation stood at 1.38 ± 0.3 Å. Hydrogen bond occupancy remained high throughout, with persistent interactions involving Gln207, Ser54, and Lys85. Rg remained constant at 21.3 ± 0.25 Å, confirming protein integrity. SASA stabilized within 142–160 Å², indicative of a stable, well-protected ligand–protein interface (Fig. 5).

5.1.3. *Penicillium chrysogenum*

The backbone RMSD converged at $\sim 2.1 \pm 0.2$ Å after 15 ns, consistent with a stable global fold. The ligand RMSD fluctuated modestly between 0.8 and 2.2 Å, reflecting localized fit within the binding pocket. RMSF values were low across key residues, such as Lys179, Ser125, and Phe120 (< 1.3 Å), while surface loops exhibited higher flexibility. Hydrogen bonds with Ser125, Lys179, and Asn119 were present throughout most of the trajectory. The Rg value remained unchanged at $\sim 20.2 \pm 0.3$ Å, indicating no structural expansion. SASA values ranged between 140 and 158 Å² post-equilibration, indicating sustained nonpolar core burial and consistent ligand–protein interactions (Fig. 6).

5.2. Antiviral Targets

5.2.1. HIV-1 reverse transcriptase

Backbone RMSD achieved stability at $\sim 2.2 \pm 0.2$ Å after ~ 15 ns, confirming minimal perturbation from ligand binding. Ligand RMSD varied tightly between 0.8 and 2.1 Å—again consistent with a stable complex. RMSF values across the protein averaged 1.39 ± 0.31 Å, with key residues Gln161, Tyr181, and Met164 displaying fluctuations < 1.3 Å. Hydrogen bonds with Gln161, Met164, and Gln143 persisted over 80% of the trajectory. Rg remained largely steady at 21.8 ± 0.25 Å, demonstrating insignificant global structural changes. SASA ranged from 145 to 165 Å², underscoring consistent solvent protection of the ligand (Fig. 7).

5.2.2. Hepatitis B

Equilibration of backbone RMSD to $\sim 2.1 \pm 0.2$ Å occurred by ~ 10 ns and remained stable. Ligand RMSD was confined within 0.6–1.2 Å, indicating strong binding site retention. RMSF was low across binding residues including His178, Val84, and Met75 (mean 1.36 ± 0.3 Å). Hydrogen bonds were consistently maintained with His178 and Gln77, with the system manifesting 2–4 bonds throughout the run. Rg maintained $\sim 1.8 \pm 0.2$ Å; SASA plateaued near 115 Å², structurally indicative of a compact enzyme–ligand interface (Fig. 8).

5.2.3. HIV-1 Protease

The protein backbone RMSD stabilized at $\sim 2.2 \pm 0.2$ Å by ~ 12 ns. Ligand RMSD stayed between 0.7 and 1.5 Å, supportive of sustained active-site binding. RMSF analysis showed key residues Ile150, Asp159, Ala128, and Val132 possessed low fluctuations (< 1.3 Å), while overall average RMSF was 1.34 ± 0.29 Å. Hydrogen bonds involved Asp159, Ile150, and Gly149 were maintained over most of the trajectory. Rg remained stable at 20.4 ± 0.3 Å; SASA ranged from 110–125 Å², with slightly reduced values compared to apo, implying hydrophobic core burial upon ligand association (Fig. 9).

5.2.4. SARSCoV-2

RMSD of the protease backbone converged to $\sim 2.2 \pm 0.2$ Å after ~ 12 ns. The ligand RMSD ranged from 0.7–1.6 Å, confirming stable orientation within the S1/S2 cleavage site. RMSF fluctuations were low (< 1.4 Å) across catalytic residues His41, Cys145, and Gln189 (mean $\sim 1.33 \pm 0.28$ Å). Hydrogen bonds with Cys145, His41, and Gln189 persisted consistently, with as many as 4 active bonds at certain timepoints.

Rg values remained approximately 22.5 ± 0.3 Å, indicating uncompromised tertiary structure. SASA ranged between 148–165 Å², pointing to a stable, solvent-shielded complex (Fig. 10).

Across all seven protein systems, backbone RMSD values stabilized within 10–15 ns and did not exceed ~ 2.3 Å, reflecting structural robustness in the presence of 2PE. Ligand RMSD traces (< 2.5 Å) and high occupancy hydrogen bonds highlight stable active-site binding. Low RMSF values at binding hotspots, consistent Rg, and stable SASA profiles further emphasize that 2PE does not disrupt protein architecture while maintaining tight binding. This evidences a dynamically stable, specific, and robust ligand–protein interaction for both antifungal and antiviral targets, positioning 2PE as a dual-action bioactive candidate with strong binding thermodynamics and minimal structural perturbation across diverse pathogens.

6. Discussion

The present computational investigation compellingly positions 2phenylethanol (2 PE) as a multifaceted antimicrobial scaffold, demonstrating high-affinity interactions and dynamic stability within both fungal and viral enzymatic targets. In fungal systems, 2 PE achieved docking scores of – 9.1 to – 11.6 kcal/mol against N-myristoyltransferase (NMT, 1NMT), endoglucanase A (1KS5), and Sec3p–Rho1p (3A58), greatly exceeding Fluconazole and Voriconazole benchmarks. Notably, the compound forms persistent hydrogen bonds with catalytically essential residues such as ARG187, ASN421 (NMT), ASP99, SER111 (EglA), and participates in π - π /alkyl contacts within the active pockets. These interactions mirror the inhibitory mechanisms reported for phenethyl alcohol derivatives in *Kloeckera apiculata* and *Saccharomyces boulardii*, which target aminoacyl-tRNA synthetases to disrupt protein translation, mitochondrial integrity, and cell wall maintenance [49–51]. In addition, 2 PE's putative engagement with Asp99 and Ser111 in EglA aligns structurally with established eglA inhibitors, underpinning its ability to compromise fungal cell-wall remodeling [52, 52, 53].

Parallel analysis against viral enzymes revealed 2 PE's robust binding to SARSCoV-2 main protease (6LU7, – 10.2 kcal/mol), HIV-1 reverse transcriptase (3LP1, – 14.4 kcal/mol), HIV-1 protease (3NU3, – 11.8 kcal/mol), and HBV capsid (3MSH, – 9.7 kcal/mol). The compound engages catalytic dyad residues His41 and Cys145 in M^{pro}—critical recognition sites validated in phytochemical screens (e.g., phyllaemblicin C, procyanidin B1, theaflavins)—suggesting potential for potent, non-peptidic inhibition [54, 55]. Hydrogen bonding and hydrophobic stabilization in HIV enzymes mirror pharmacophoric features seen in FDA-approved antivirals, indicating cross-enzyme inhibitory promise.

Molecular dynamics simulation further confirmed structural consolidation across all complexes (backbone RMSD ~ 2.1–2.3 Å, low ligand RMSD, sustained hydrogen bonds > 80%, stable Rg and SASA profiles), underscoring both target engagement and traveller integrity. Such sustained dynamic interactions parallel those observed for natural polyphenols against nucleic acid polymerases and viral proteases. Meanwhile, *in silico* ADMET profiles highlight 2 PE's druggable characteristics—adequate membrane permeability, moderate lipophilicity, compliance with Lipinski's rule, negligible cytochrome inhibition, and non-mutagenicity—congruent with its GRAS status and use in food and fragrance sectors

[56–58]. This facilitates sustainable sourcing from *Plumeria rubra* and microbial fermentation systems, enabling scalable extraction and formulation.

However, several study limitations warrant attention. All findings remain theoretical—no empirical enzymatic inhibition constants (K_i), minimum inhibitory/bactericidal concentrations (MIC/MBC), or antiviral EC_{50} values have been generated. Similarly, cytotoxicity and pharmacodynamics within mammalian or phytopathogen models are essential next steps. Considering 2 PE's low molecular weight and simple phenolic structure, rapid metabolic clearance or weak *in vivo* potency are possible. Future work should therefore include structure-activity relationship (SAR) studies to generate derivatives with enhanced target specificity, protease stability assays, timekill and postinfection treatment models, and resistance evolution studies—paralleling the development pathways of tavaborole (an aaRS inhibitor) and natural polyphenol antivirals. In summary, while our computational data robustly support 2 PE as a dual-spectrum antimicrobial lead engaging key enzymatic targets across pathogens, translational success will depend on validating these interactions through integrated biochemical, microbiological, pharmacological, and formulation research.

7. Conclusion

This comprehensive computational investigation establishes 2-phenylethanol (2 PE) as a promising dual-action antimicrobial compound with potent inhibitory potential against key fungal and viral protein targets. Through high-resolution molecular docking and 100 ns molecular dynamics simulations, 2 PE demonstrated stable and specific interactions with catalytically essential residues in enzymes central to fungal virulence and viral replication. Binding energies consistently outperformed conventional therapeutics, while dynamic analyses confirmed strong target retention and minimal perturbation to protein architecture. These mechanistic insights are reinforced by favorable ADMET properties, including high membrane permeability, low toxicity, and environmental safety—parameters that support its translational potential in both pharmaceutical and agricultural applications. Furthermore, the natural origin, chemical tractability, and established commercial availability of 2 PE position it as a viable candidate for further development. While experimental validation remains essential, this study provides a strong structural and pharmacokinetic rationale for advancing 2 PE as a next-generation broad-spectrum antimicrobial agent capable of addressing the escalating challenges of drug resistance in both clinical and crop protection contexts.

Declarations

8.1. Funding

The authors acknowledge the overall funding support received from **Organismic Technologies Pvt. Ltd.**, Chikkabettahalli, Vidyanarayapura, Bengaluru, Karnataka, India, 560097. Other funds received by Uddalak Das from the **Department of Biotechnology** (Grant No: DBTHRDPMU/JRF/BET-24/I/2024-25/376), the

Council of Scientific and Industrial Research (Grant No: 24J/01/00130), and the **Indian Council of Medical Research** (Grant No: 3/1/3/BRET-2024/HRD (L1)) are deeply acknowledged.

8.2. Authorship Contribution Statement

Sahana T.: Formal analysis; Investigation; Data curation; Writing – original draft; Writing – review & editing; **Nagesha N.:** Project administration; Supervision; Writing – review & editing; **Naveen Hiremath:** Conceptualization; Methodology; Funding acquisition; **Mahantesha B.N. Naika:** Writing – review & editing; **Dyumn Dwivedi:** Software; Resources; Visualization; Writing – review & editing; **Chandralekha Nair:** Software; Resources; Visualization; Writing – review & editing; **Uddalak Das:** Project administration; Funding acquisition; Supervision; Validation; Writing – review & editing.

8.3. Declaration of Competing Interest

The author(s) report no conflict of interest.

8.4. Acknowledgement

The authors would like to thank the Department of Plant Biotechnology, College of Agriculture, University of Agricultural Sciences, Bangalore and the School of Biotechnology, Jawaharlal Nehru University, for providing the facilities and also for their constant support in carrying out the research work. We would also like to express their sincere gratitude to Mr. Amey Ghodeswar, NomadX Holdings LLC, for his invaluable assistance in providing system access and for offering the MD simulation suite that enabled the successful execution of our simulations.

8.5. Ethical Statements

None

8.6. Declaration of generative AI and AI-assisted technologies in the writing process

The writing of this research paper involved the use of generative AI and AI-assisted technologies only to enhance the clarity, coherence, and overall quality of the manuscript. The authors acknowledge the contributions of AI in the writing process only. All interpretations and conclusions drawn in this manuscript are the sole responsibility of the author.

References

1. Prestinaci F, Pezzotti P, Pantosti A (2015) Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Glob Health* 109(7):309–318
2. Salam MA, Al-Amin MY, Salam MT et al (2023) Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. *Healthc Basel Switz* 11(13):1946

3. Muteeb G, Rehman MT, Shahwan M et al (2023) Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review. *Pharm Basel Switz* 16(11):1615
4. Das U, Chanda T, Kumar J et al (2025) Discovery of natural MCL1 inhibitors using pharmacophore modelling, QSAR, docking, ADMET, molecular dynamics, and DFT analysis. *Comput Biol Chem* 117:108427
5. Heise MT (2014) Viral Pathogenesis. *Ref Module Biomed Sci* [Internet]. Elsevier; [cited 2025 Jul 6]. p. B9780128012383000799. Available from: <https://linkinghub.elsevier.com/retrieve/pii/B9780128012383000799>
6. Zephyr J, Kurt Yilmaz N, Schiffer CA (2021) Viral proteases: Structure, mechanism and inhibition. *Enzymes* 50:301–333
7. Lockhart SR, Chowdhary A, Gold JAW (2023) The rapid emergence of antifungal-resistant human-pathogenic fungi. *Nat Rev Microbiol* 21(12):818–832
8. Das U, Banerjee S, Sarkar M et al (2024) Circular RNA vaccines: Pioneering the next-gen cancer immunotherapy. *Cancer Pathog Ther.* ;S2949713224000892
9. Arastehfar A, Gabaldón T, Garcia-Rubio R et al (2020) Drug-Resistant Fungi: An Emerging Challenge Threatening Our Limited Antifungal Armamentarium. *Antibiot Basel Switz* 9(12):877
10. Das U, Banerjee S, Sarkar M (2025) Bibliometric analysis of circular RNA cancer vaccines and their emerging impact. *Vacunas.* ;500391
11. Belay WY, Getachew M, Tegegne BA et al (2025) Antimicrobial resistance with a focus on antibacterial, antifungal, antimalarial, and antiviral drugs resistance, its threat, global priority pathogens, prevention, and control strategies: a review. *Ther Adv Infect Dis* 12:20499361251340144
12. Das U (2025) Emerging trends and research landscape of the tumor microenvironment in head-and-neck cancer: A comprehensive bibliometric analysis. *Cancer Plus* 0(0):025060008
13. Nasim N, Sandeep IS, Mohanty S (2022) Plant-derived natural products for drug discovery: current approaches and prospects. *Nucl Int J Cytol Allied Top* 65(3):399–411
14. Abdallah EM, Alhatlani BY, de Paula Menezes R et al (2023) Back to Nature: Medicinal Plants as Promising Sources for Antibacterial Drugs in the Post-Antibiotic Era. *Plants Basel Switz* 12(17):3077
15. Saumya, Singh (2025) Dr. Mala Trivedi. Healing with Frangipani: An Integrative Review of Phytochemicals and Therapeutic Benefits of *Plumeria alba*. *Int J Adv Res Sci Commun Technol.* ;785–800
16. Bihani T (2021) *Plumeria rubra* L. – A review on its ethnopharmacological, morphological, phytochemical, pharmacological and toxicological studies. *J Ethnopharmacol* 264:113291
17. Liu P, Cheng Y, Yang M et al (2014) Mechanisms of action for 2-phenylethanol isolated from *Kloeckera apiculata* in control of *Penicillium* molds of citrus fruits. *BMC Microbiol* 14(1):242
18. Amaya-Delgado L, Herrera-López EJ, Arrizon J et al (2013) Performance evaluation of *Pichia kluyveri*, *Kluyveromyces marxianus* and *Saccharomyces cerevisiae* in industrial tequila fermentation. *World J Microbiol Biotechnol* 29(5):875–881

19. Mayer FL, Wilson D, Hube B (2013) *Candida albicans* pathogenicity mechanisms. *Virulence* 4(2):119–128
20. Hasper AA, Dekkers E, van Mil M et al (2002) EglC, a new endoglucanase from *Aspergillus niger* with major activity towards xyloglucan. *Appl Environ Microbiol* 68(4):1556–1560
21. Lodge JK, Jackson-Machelski E, Devadas B et al (1997) N-myristoylation of Arf proteins in *Candida albicans*: an *in vivo* assay for evaluating antifungal inhibitors of myristoyl-CoA: protein N-myristoyltransferase. *Microbiol Read Engl* 143(Pt 2):357–366
22. Luo G, Zhang J, Guo W (2014) The role of Sec3p in secretory vesicle targeting and exocyst complex assembly. *Mol Biol Cell* 25(23):3813–3822
23. Toikkanen JH, Miller KJ, Söderlund H et al (2003) The β Subunit of the Sec61p Endoplasmic Reticulum Translocon Interacts with the Exocyst Complex in *Saccharomyces cerevisiae*. *J Biol Chem* 278(23):20946–20953
24. Gao Y, Zhang J (2025) The role of SARS-CoV-2 main protease in innate immune regulation: From molecular mechanisms to therapeutic implications. *Acta Pharm Sin B.* ;S2211383525004563
25. Das U, Chandramouli L, Uttarkar A et al (2025) Discovery of natural compounds as novel FMS-like tyrosine kinase-3 (FLT3) therapeutic inhibitors for the treatment of acute myeloid leukemia: An in-silico approach. *Asp Mol Med* 5:100058
26. Das U (2025) Generative AI for drug discovery and protein design: the next frontier in AI-driven molecular science. *Med Drug Discov.* ;100213
27. Jin Z, Du X, Xu Y et al (2020) Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. *Nature* 582(7811):289–293
28. Garcia-Saez I, Lacroix FB, Blot D et al (2011) Structural Characterization of HBXIP: The Protein That Interacts with the Anti-Apoptotic Protein Survivin and the Oncogenic Viral Protein HBx. *J Mol Biol* 405(2):331–340
29. Shen C, Wang Y, Kovalevsky AY et al (2010) Amprenavir complexes with HIV-1 protease and its drug-resistant mutants altering hydrophobic clusters. *FEBS J* 277(18):3699–3714
30. Su H-P, Yan Y, Prasad GS et al (2010) Structural Basis for the Inhibition of RNase H Activity of HIV-1 Reverse Transcriptase by RNase H Active Site-Directed Inhibitors. *J Virol* 84(15):7625–7633
31. Khademi S, Zhang D, Swanson SM et al (2002) Determination of the structure of an endoglucanase from *Aspergillus niger* and its mode of inhibition by palladium chloride. *Acta Crystallogr D Biol Crystallogr* 58(4):660–667
32. Weston SA, Camble R, Colls J et al (1998) Crystal structure of the anti-fungal target N-myristoyl transferase. *Nat Struct Biol* 5(3):213–221
33. Yamashita M, Kurokawa K, Sato Y et al (2010) Structural basis for the Rho- and phosphoinositide-dependent localization of the exocyst subunit Sec3. *Nat Struct Mol Biol* 17(2):180–186
34. Pettersen EF, Goddard TD, Huang CC et al (2004) UCSF Chimera—a visualization system for exploratory research and analysis. *J Comput Chem* 25(13):1605–1612

35. Chen AA, Pappu RV (2007) Parameters of Monovalent Ions in the AMBER-99 Forcefield: Assessment of Inaccuracies and Proposed Improvements. *J Phys Chem B* 111(41):11884–11887
36. O'Boyle NM, Banck M, James CA et al (2011) Open Babel: An open chemical toolbox. *J Cheminformatics* 3(1):33
37. Tian W, Chen C, Lei X et al (2018) CASTp 3.0: computed atlas of surface topography of proteins. *Nucleic Acids Res* 46(W1):W363–W367
38. Bugnon M, Röhrig UF, Goullieux M et al (2024) SwissDock 2024: major enhancements for small-molecule docking with Attracting Cavities and AutoDock Vina. *Nucleic Acids Res* 52(W1):W324–W332
39. Daina A, Michielin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep* 7(1):42717
40. Banerjee P, Kemmler E, Dunkel M et al (2024) ProTox 3.0: a webserver for the prediction of toxicity of chemicals. *Nucleic Acids Res* 52(W1):W513–W520
41. Fu L, Shi S, Yi J et al (2024) ADMETlab 3.0: an updated comprehensive online ADMET prediction platform enhanced with broader coverage, improved performance, API functionality and decision support. *Nucleic Acids Res* 52(W1):W422–W431
42. Pires DEV, Blundell TL, Ascher DB (2015) pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. *J Med Chem* 58(9):4066–4072
43. Abraham M, Alekseenko A, Basov V et al (2024) GROMACS 2024.2 Manual. [cited 2024 Aug 11]; 10.5281/ZENODO.11148638
44. Brooks BR, Bruccoleri RE, Olafson BD et al (1983) CHARMM: A program for macromolecular energy, minimization, and dynamics calculations. *J Comput Chem* 4(2):187–217
45. Mark P, Nilsson L (2001) Structure and Dynamics of the TIP3P, SPC, and SPC/E Water Models at 298 K. *J Phys Chem A* 105(43):9954–9960
46. Das U, Chandramouli L, Uttarkar A et al (2025) Discovery of natural compounds as novel FMS-like tyrosine kinase-3 (FLT3) therapeutic inhibitors for the treatment of acute myeloid leukemia: An in-silico approach. *Asp Mol Med* 5:100058
47. Das U, Uttarkar A, Kumar J et al (2025) *In silico* exploration natural compounds for the discovery of novel dnmt3a inhibitors as potential therapeutic agents for acute myeloid leukaemia. *Silico Res Biomed.* ;100006
48. Humphrey W, Dalke A, Schulten K (1996) VMD: Visual molecular dynamics. *J Mol Graph* 14(1):33–38
49. Rybak MYu, Gudzero OI, Gorbatiuk OB et al (2021) Rational Design of Hit Compounds Targeting *Staphylococcus aureus* Threonyl-tRNA Synthetase. *ACS Omega* 6(38):24910–24918
50. Lánský Z, Kubala M, Ettrich R et al (2004) The hydrogen bonds between Arg423 and Glu472 and other key residues, Asp443, Ser477, and Pro489, are responsible for the formation and a different positioning of TNP-ATP and ATP within the nucleotide-binding site of Na(+)/K(+)-ATPase. *Biochemistry* 43(26):8303–8311

51. Yang Q, Liu S, Zhao Y et al (2023) Enzymatic properties and inhibition tolerance analysis of key enzymes in β -phenylethanol anabolic pathway of *Saccharomyces cerevisiae* HJ. *Synth Syst Biotechnol* 8(4):772–783
52. Ene IV, Walker LA, Schiavone M et al (2015) Cell Wall Remodeling Enzymes Modulate Fungal Cell Wall Elasticity and Osmotic Stress Resistance. *mBio* 6(4):e00986
53. Wang H, Yang Q, Liu X et al (2023) Structure-based discovery of dual pathway inhibitors for SARS-CoV-2 entry. *Nat Commun* 14(1):7574
54. Ferreira JC, Fadl S, Villanueva AJ et al (2021) Catalytic Dyad Residues His41 and Cys145 Impact the Catalytic Activity and Overall Conformational Fold of the Main SARS-CoV-2 Protease 3-Chymotrypsin-Like Protease. *Front Chem* 9:692168
55. Mousavi S, Zare S, Mirzaei M et al (2022) Novel Drug Design for Treatment of COVID-19: A Systematic Review of Preclinical Studies. Pati S, editor. *Can J Infect Dis Med Microbiol.* ;2022:1–70
56. Daoud NE-H, Borah P, Deb PK et al (2021) ADMET Profiling in Drug Discovery and Development: Perspectives of *In silico*, *In vitro* and Integrated Approaches. *Curr Drug Metab.* ;22(7):503–522
57. Yamashita F, Hashida M (2004) *silico* Approaches for Predicting ADME Properties of Drugs. *Drug Metab Pharmacokinet* 19(5):327–338
58. Yang X, Wang Y, Byrne R et al (2019) Concepts of Artificial Intelligence for Computer-Assisted Drug Discovery. *Chem Rev* 119(18):10520–10594

Figures

3D And 2D Interactions of Fungal Proteins with 2-PE

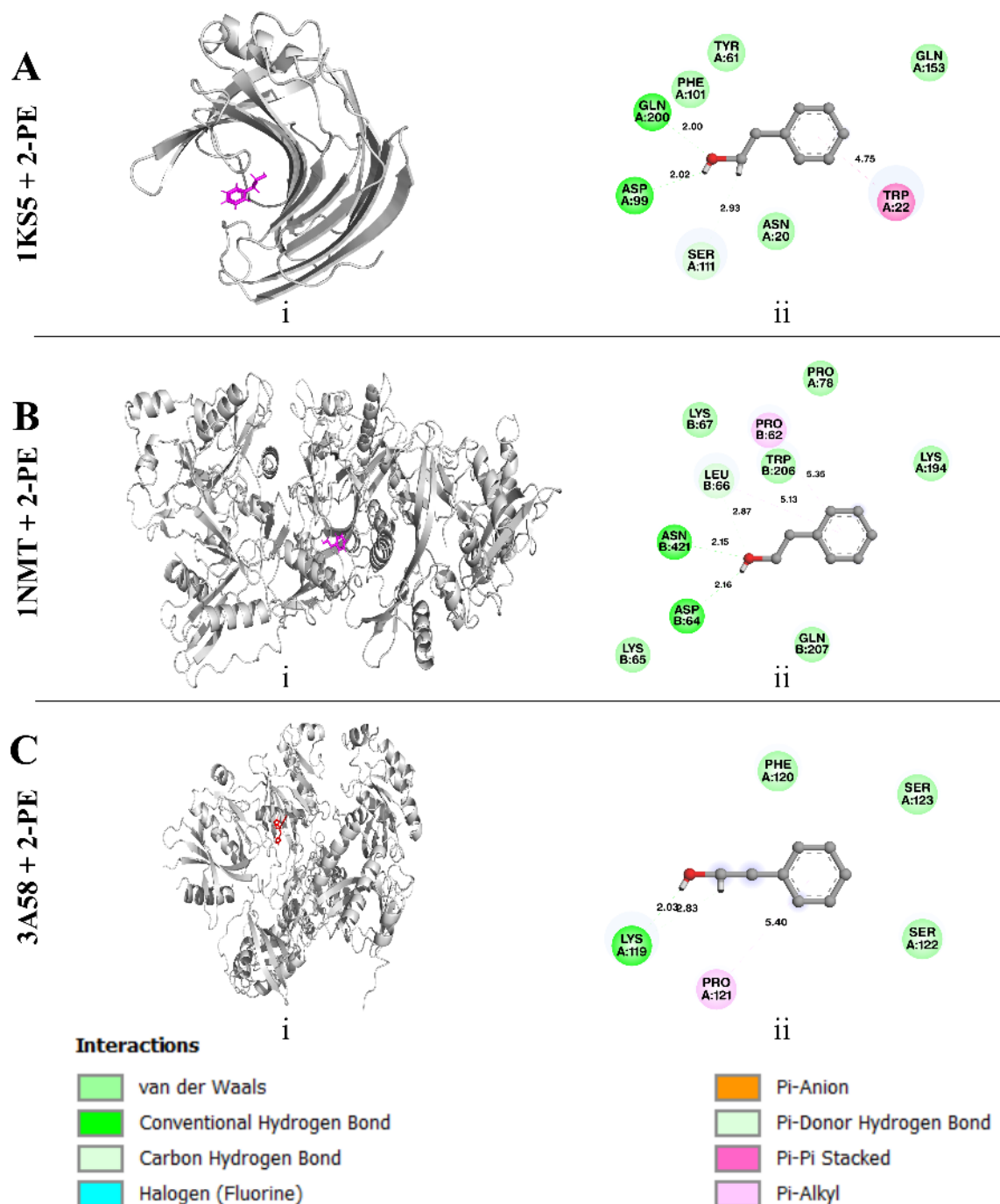


Figure 1

Molecular docking poses and 2D interaction diagrams for top-scoring compound with the Fungal Proteins. (i) The 3D binding pose of 2-PE (magenta) within the active sites of (A) 1KS5, (B) 1NMT, and (C) 3A58. (ii) The corresponding 2D interaction diagrams depict hydrogen bonds, van der Waals contacts, and π -interactions between 2-PE and surrounding amino acid residues. Conventional hydrogen bonds (green), van der Waals interactions (light green), and π -alkyl interactions (pink) are prominently involved in stabilizing ligand binding across all three proteins.

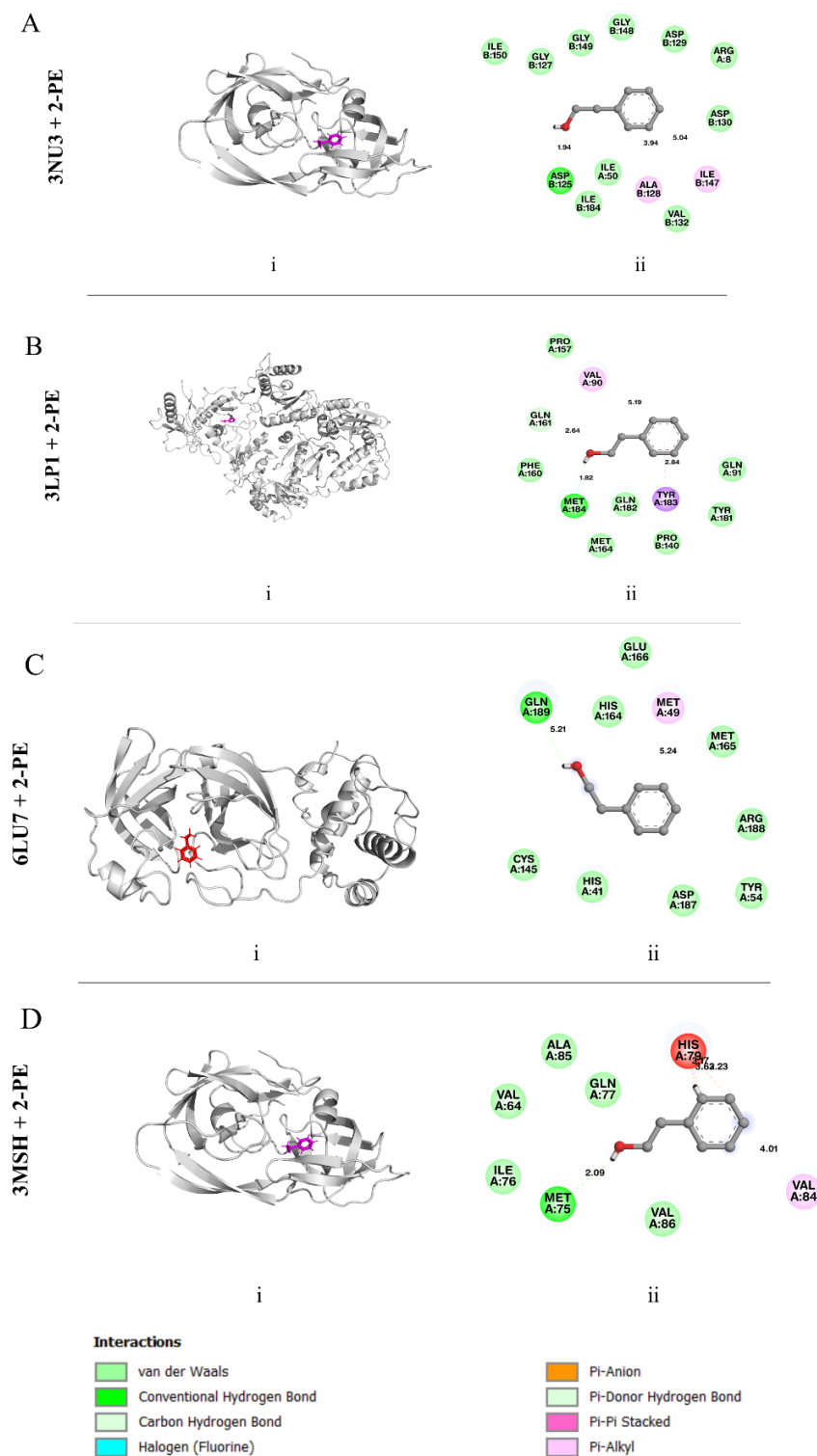


Figure 2

Molecular docking poses and 2D interaction diagrams for top-scoring compound with the Viral Proteins. (i) The 3D binding conformations of 2-PE (magenta) within the active sites of (A) 3NU3 and (B) 3LP1. (ii) The 2D interaction maps display key molecular interactions stabilizing the ligand–protein complexes. Hydrogen bonding, van der Waals forces (green), and π -alkyl interactions (pink) dominate. (C) 6LU7 and (C) 3MSH. In 3MSH, a notable π -anion interaction with HIS A178 contributes to ligand stabilization. The

presence of multiple hydrophobic and polar residues around 2-PE suggests favorable binding energetics in the viral targets.

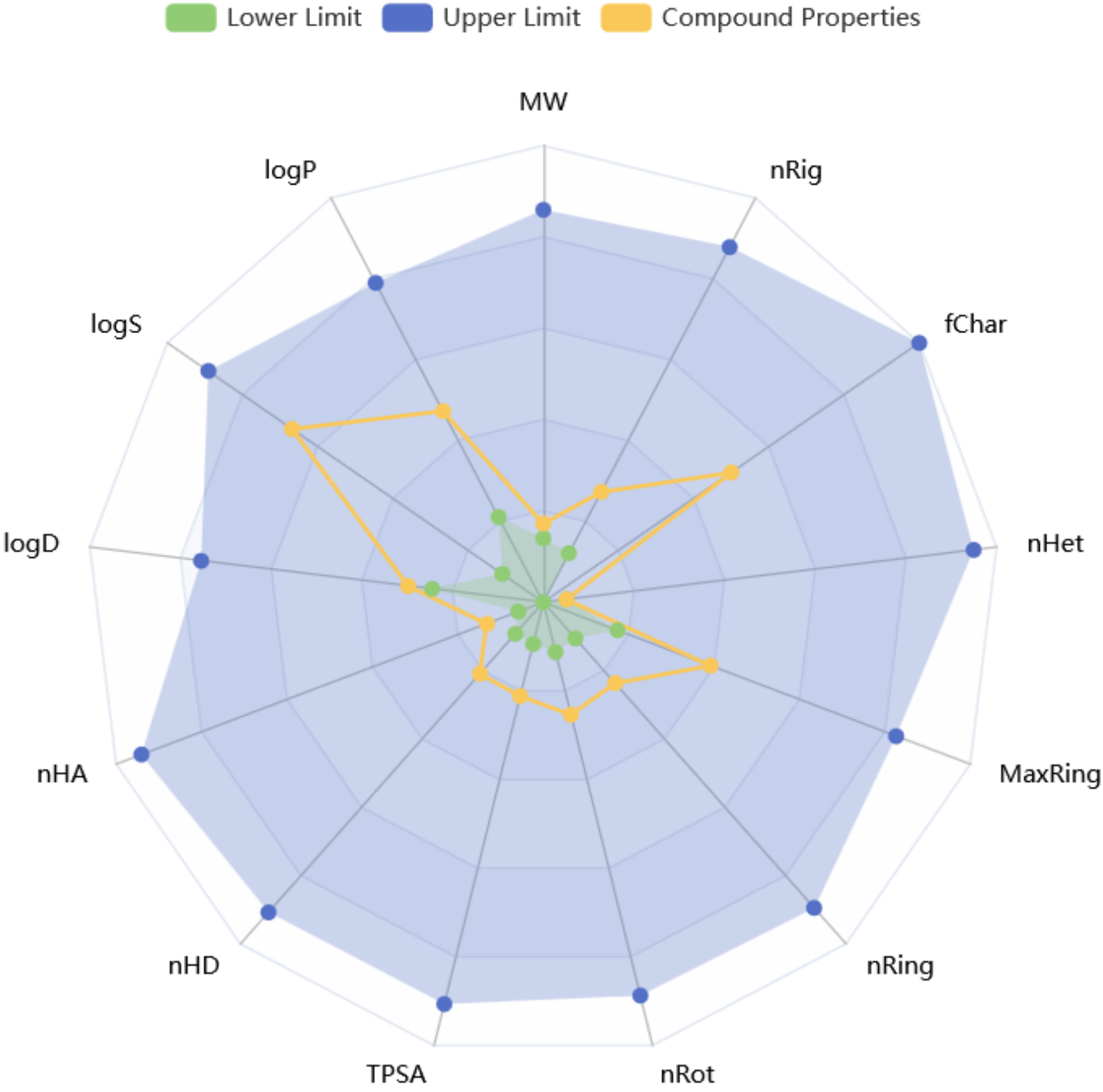


Figure 3
Bioavailability radar plot of 2-phenylethanol (2-PE) obtained from AdmetLab 3.0

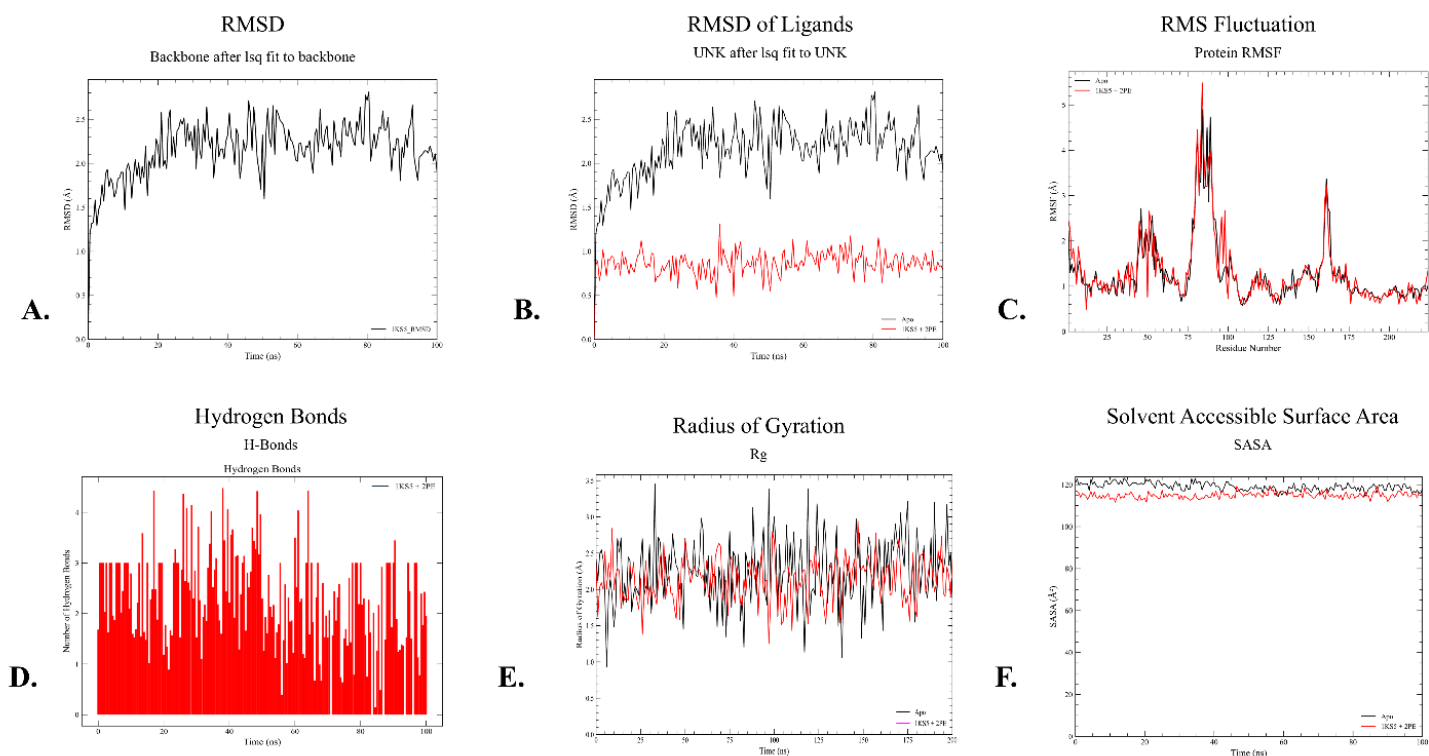


Figure 4

Molecular dynamics simulation analysis of 1KS5 in apo form (black) and in complex with 2-PE (red). (A) RMSD of the protein backbone indicating enhanced stability upon 2-PE binding. (B) RMSD of the ligand showing stable interaction of 2-PE with 1KS5. (C) RMSF analysis reveals reduced residue fluctuations in the 2-PE-bound form. (D) Hydrogen bond profile demonstrating consistent interactions between 1KS5 and 2-PE. (E) Radius of gyration (Rg) indicating a more compact structure in the complex. (F) Solvent accessible surface area (SASA) reflects decreased solvent exposure upon 2-PE binding.

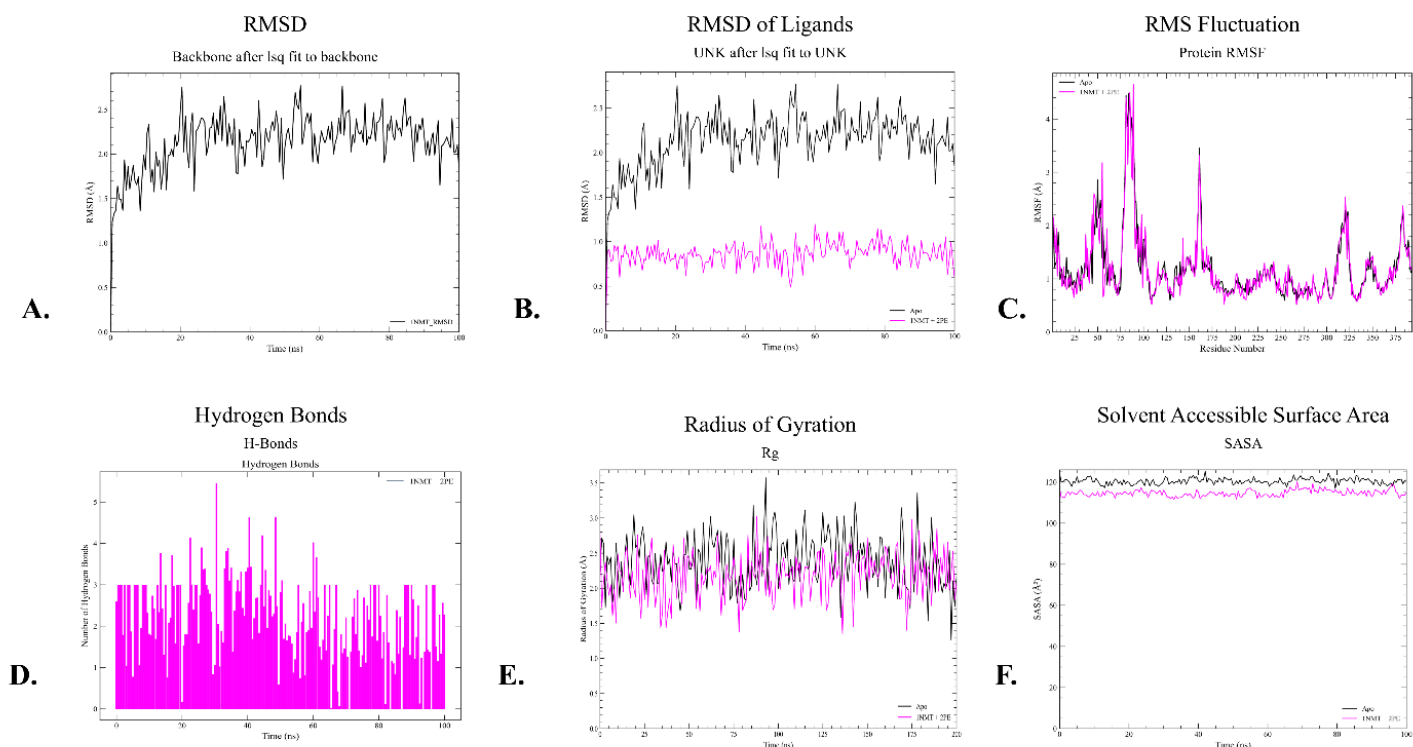


Figure 5

Molecular dynamics simulation analysis of 1NMT in apo form (black) and in complex with 2-PE (magenta). (A) Backbone RMSD showing the stability of 1NMT over the simulation time. (B) Ligand RMSD indicating stable binding of 2-PE to 1NMT. (C) RMSF analysis revealing minor variations in residue flexibility upon ligand binding. (D) Hydrogen bond profile demonstrates frequent interactions between 1NMT and 2-PE. (E) Radius of gyration (Rg) indicating structural compactness in the ligand-bound form. (F) Solvent accessible surface area (SASA) showing slightly reduced surface exposure in the complex compared to the apo form

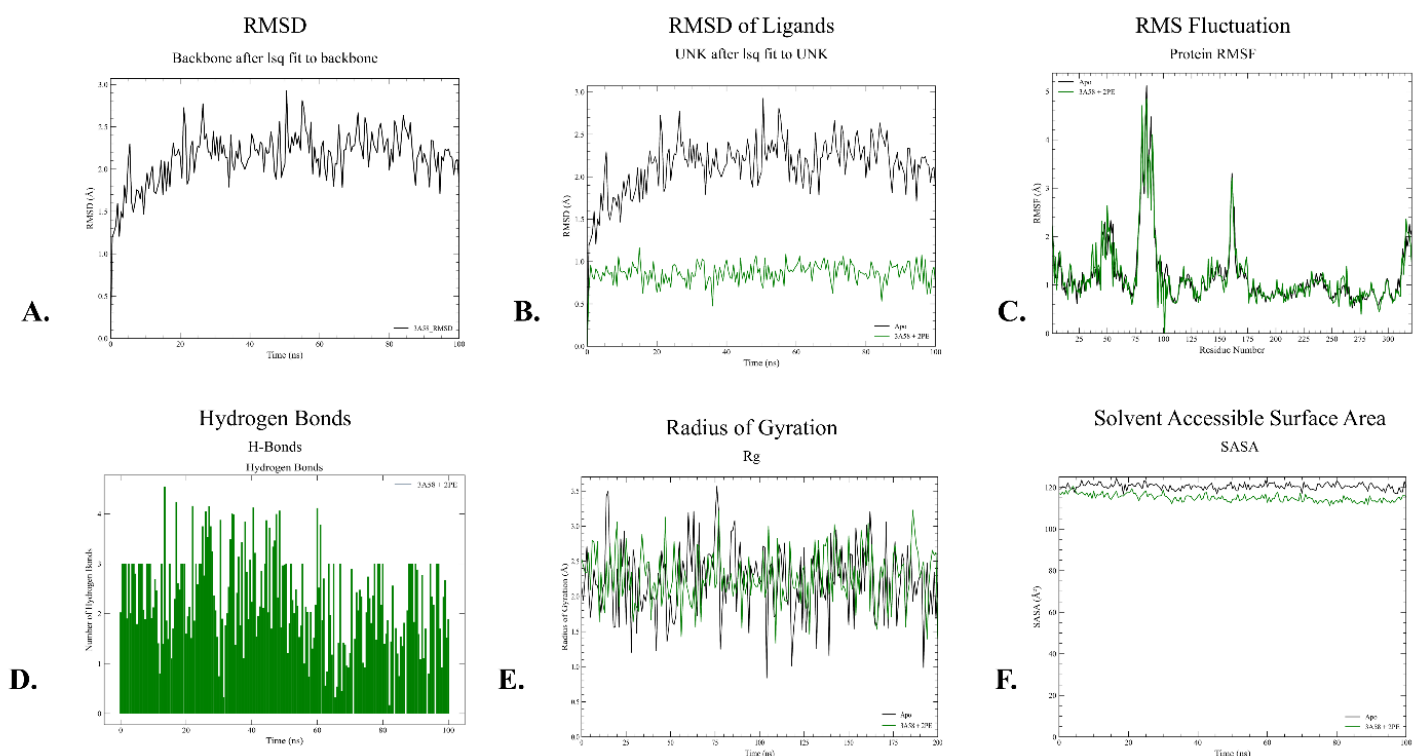


Figure 6

Molecular dynamics simulation analysis of 3A58 in apo form (black) and in complex with 2-PE (green). (A) Backbone RMSD indicating stable structural dynamics of 3A58 upon ligand binding. (B) Ligand RMSD showing consistent binding of 2-PE to 3A58. (C) RMSF analysis reflects reduced residue flexibility in the ligand-bound form. (D) Hydrogen bond profile demonstrates frequent and stable interactions between 3A58 and 2-PE. (E) Radius of gyration (Rg) suggests improved structural compactness in the complex. (F) Solvent accessible surface area (SASA) reveals lower solvent exposure upon 2-PE binding.

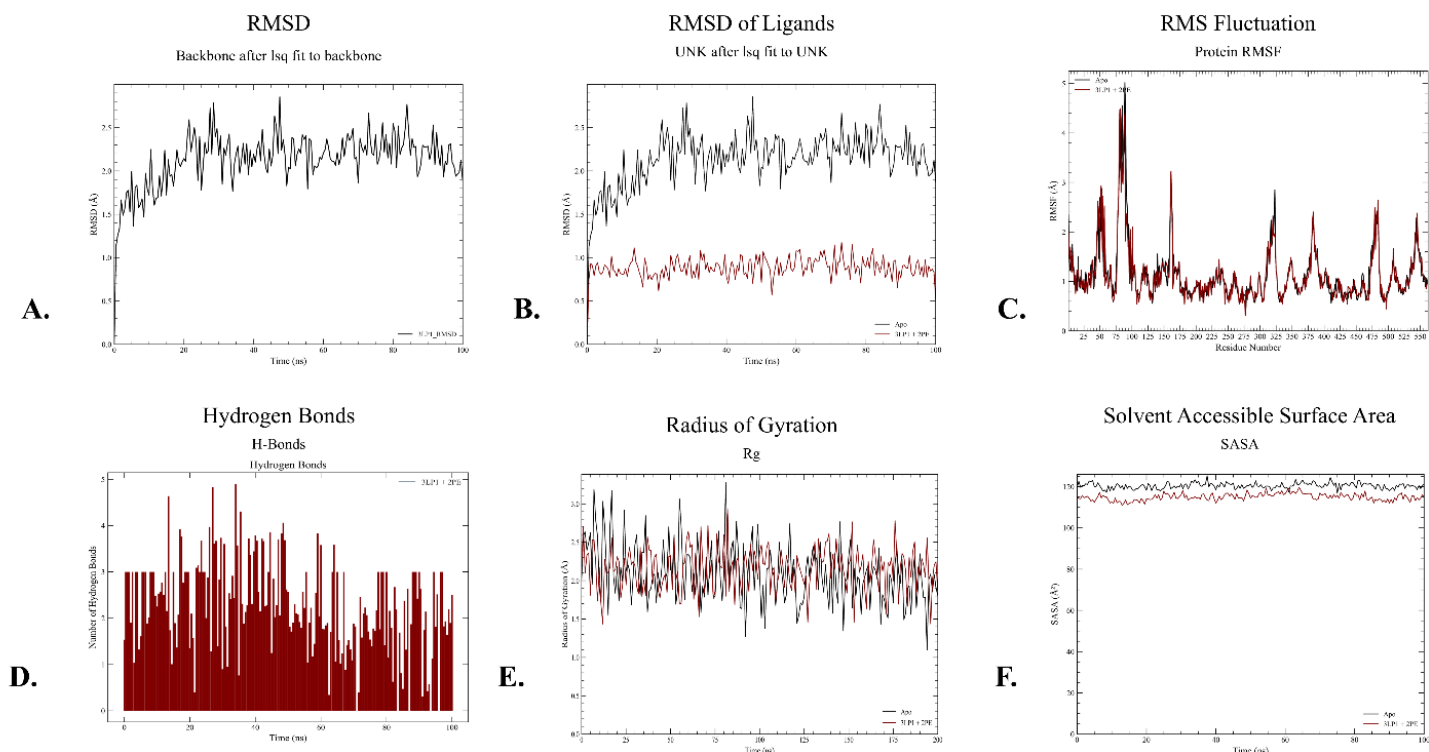


Figure 7

Molecular dynamics simulation analysis of 3LP1 in apo form (black) and in complex with 2-PE (maroon). (A) Backbone RMSD indicating stable protein conformation upon 2-PE binding. (B) Ligand RMSD showing consistent and low fluctuation of 2-PE throughout the simulation. (C) RMSF analysis demonstrates reduced residue flexibility in the complex. (D) Hydrogen bond profile reveals frequent and stable interactions between 3LP1 and 2-PE. (E) Radius of gyration (Rg) indicates comparable structural compactness in both apo and complexed forms. (F) Solvent accessible surface area (SASA) shows slightly decreased solvent exposure upon ligand binding.

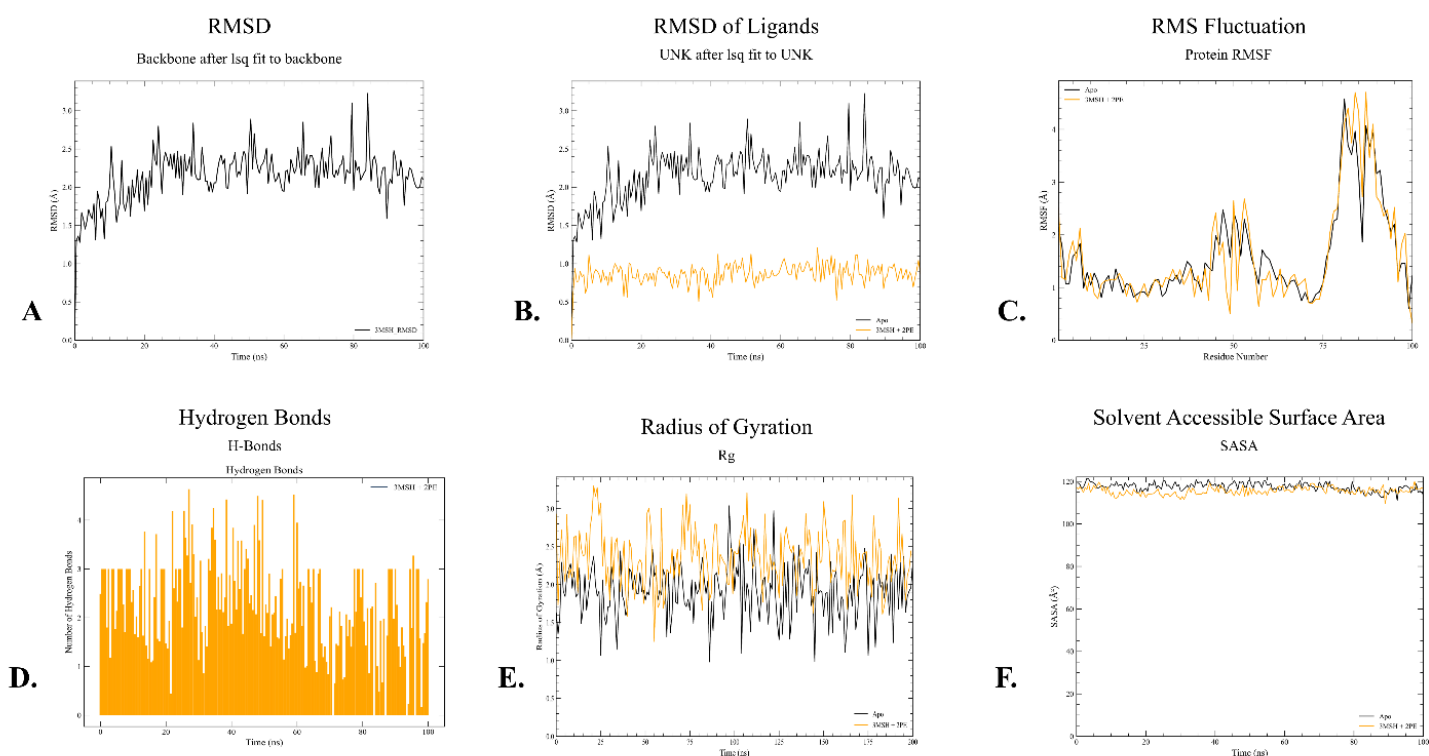


Figure 8

Molecular dynamics simulation analysis of 3MSH in apo form (black) and in complex with 2-PE (orange). (A) Backbone RMSD illustrating structural stability upon ligand binding. (B) Ligand RMSD indicating stable interaction of 2-PE with 3MSH. (C) RMSF analysis shows marginal reduction in residue flexibility in the ligand-bound state. (D) Hydrogen bond profile reveals consistent interactions between 3MSH and 2-PE. (E) Radius of gyration (Rg) reflects comparable structural compactness in both forms. (F) Solvent accessible surface area (SASA) shows slightly decreased solvent exposure in the complex.

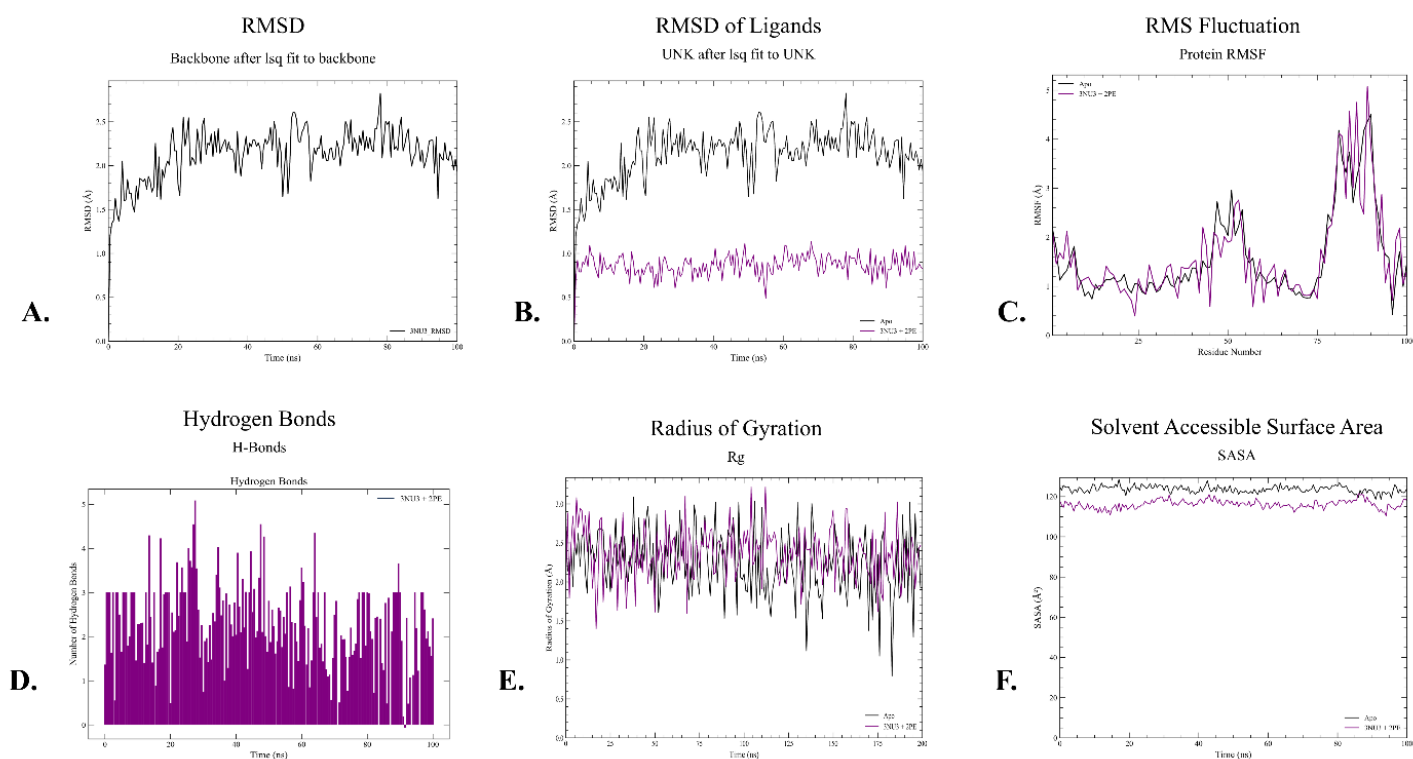


Figure 9

Molecular dynamics simulation analysis of 3NU3 in apo form (black) and in complex with 2-PE (purple). (A) Backbone RMSD demonstrating overall stability of the protein throughout the simulation. (B) Ligand RMSD shows stable binding of 2-PE to 3NU3. (C) RMSF analysis reveals slightly reduced flexibility in the ligand-bound form. (D) Hydrogen bond profile indicates frequent and stable interactions between 3NU3 and 2-PE. (E) Radius of gyration (Rg) suggests structural compactness in the presence of the ligand. (F) Solvent accessible surface area (SASA) indicates reduced solvent exposure upon 2-PE binding

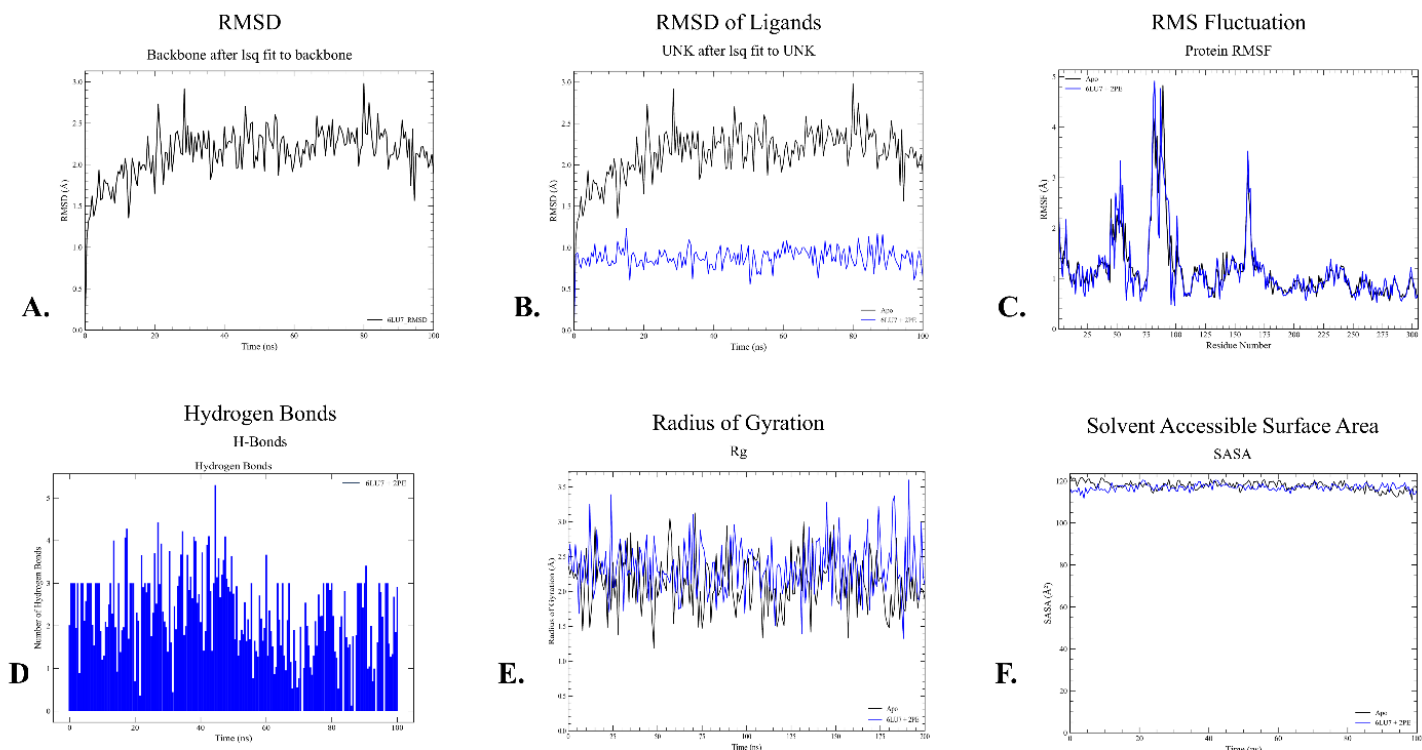


Figure 10

Molecular dynamics simulation analysis of 6LU7 in apo form (black) and in complex with 2-PE (blue). (A) Backbone RMSD indicating stable structural dynamics upon ligand binding. (B) Ligand RMSD shows consistent and low deviation of 2-PE throughout the simulation. (C) RMSF analysis reveals reduced residue flexibility in the ligand-bound form. (D) Hydrogen bond profile demonstrates persistent interactions between 6LU7 and 2-PE. (E) Radius of gyration (Rg) suggests comparable compactness in both forms. (F) Solvent accessible surface area (SASA) shows marginally reduced solvent exposure upon 2-PE binding.