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Molecular Docking Studies of *Nyctanthes arbor-tristis* Phytochemicals for Targeting TNF Receptor in Arthritis

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Abstract

Rheumatoid Arthritis is an autoimmune disorder which results in inflammation. Tumor necrosis factor-alpha (TNF-α) is responsible for the progression of inflammatory arthritis by promoting immune cell activation and cytokine release. The present study explores the potential of bioactive compounds derived from Nyctanthes arbor-tristis (Parijat) in modulating TNF receptor activity through molecular docking. Computational methods were employed to evaluate the binding affinity of selected phytocompounds from N. arbor-tristis against the extracellular domain of the TNF receptor. Molecular docking was performed using PyRx, and the pharmacokinetic properties of the ligands were analyzed using ADMET filters to assess their drug-like potential. Molecular docking analysis revealed that the ligands Decan-1-ol, 1,3-Distearin, and 2,3,4,6-Tetramethyl-D-Glucose demonstrated the highest binding affinity toward the 1ext protein, indicating their strong potential for receptor interaction. Further in vitro study is needed to confirm their effectiveness.

Keywords: Nyctanthes arbor-tristis, arthritis, tumor necrosis factor receptor, molecular docking, phytochemicals, computational screening, ADMET analysis

INTRODUCTION

Rheumatoid arthritis is an inflammatory disease that primarily affects the synovial lining of the joints which in turn causes stiffness, pain, and swelling [1]. TNF-α is produced by immune cells like macrophages [2]. It triggers a series of intracellular signaling pathways that result in pro-inflammatory reactions by binding to its receptors, TNFR1 and TNFR2, which are present on the surface of several cells. To draw additional immune cells, such as T cells, neutrophils, and monocytes, to the site of inflammation, then TNF-α stimulates the release of chemokines, IL-1, IL-6, and other cytokines, which causes chronic inflammation and tissue damage [3, 4].

Nyctanthes arbor-tristis commonly known as night jasmine belongs to the Oleaceae family, which has significant therapeutic properties in Ayurveda [5–7]. The various parts of plant have been used for treatment of number of illnesses. This plant exhibits diverse pharmacological properties like anti-viral, antifungal, anti-pyretic, anti-allergic, and immunomodulatory properties [8]. Extracts of *Nyctanthes arbor-tristis* has been reported to show anti-inflammatory properties [9, 10]. Targeting important molecular pathways in inflammatory illnesses, especially TNF receptor-mediated signaling in arthritis, could be possible by the plant's diverse phytochemical profile.

Computational drug discovery techniques, like molecular docking, can be used for identification of potential drug by predicting interaction between protein and phytochemicals from plants. This study has been conducted to screen the number of compounds from *Nyctanthes arbor-tristis* against

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TNF Receptor to access binding affinity of phytocompounds against receptor protein and to screen phytocompounds for their drug likeness properties. Findings of this study could lead to screening of bioactive compounds as drug which will show anti-inflammatory properties and pave us way for in-vivo experiments for treatment of rheumatoid arthritis.

METHODS

Retrieval of Ligands from Database

The Osadhi database (https://neist.res.in/osadhi/index.html) was utilized to identify potential ligands, which returned a set of 12 ligands [11]. The canonical SMILES of these ligands were recorded, and they were retrieved in SDF format from PubChem (https://pubchem.ncbi.nlm.nih.gov/) [12].

Retrieval of Proteins from PDB Database

The Crystal structure of extracellular domain of the 55kda tumor necrosis factor receptor (signaling protein) with PDB ID 1EXT was downloaded from the PDB databank (https://www.rcsb.org/structure/1EXT) [13]. The protein was downloaded in PDB format. The resolution of the protein downloaded is 1.85 Å and the method of retrieval of the protein is X-ray diffraction.

Protein Purification

The protein 1EXT was purified by eliminating water molecules, as the free energy of water does not align with its crystallographic structure. All water molecules were removed prior to docking, as they could interfere with the docking results. Both chains of proteins were preserved for analysis to ensure a thorough investigation of the structure. The prebound heteroatoms and any complex ligands were also discarded. To improve the quality of the purified structure, polar hydrogen atoms were added, and the final purified structure was saved as a .pdb file for docking analysis. The purification procedure was performed using BIOVIA Discovery Studio (Figure 1) [14].

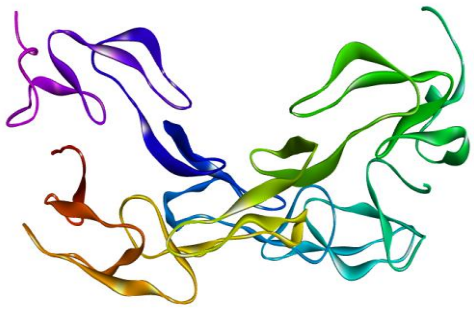

Figure 1. Purified structure of protein 1 EXT.

Ramachandran Plot Analysis for Protein Study

Ramachandran plot is used to study the structure and quality of protein. This plot gives us details about torsion angles, i.e., phi and psi in protein. Secondary structure prediction and Ramachandran plot analysis of the purified 1EXT protein were conducted using the webserver known as SAVE (https://saves.mbi.ucla.edu/) [15, 16] and PDBSum Generate (https://www.ebi.ac.uk/thornton-srv/databases/pdbsum/Generate.html) [17].

Pharmacological Studies of Ligands

SwissADME (http://www.swissadme.ch/) analysis was utilized to assess the pharmacological properties of the ligands based on their physicochemical parameters, including lipophilicity, saturation, insolubility, flexibility, size, and polarity [18, 19]. The ligands were then screened using the LIPINSKI rule of 5 to ensure their drug-likeness [20]. From the Osadhi database, 12 compounds were obtained and evaluated. Three compounds were ruled out based on the LIPINSKI criteria, as well as considerations of high gastrointestinal absorption and bioavailability. ADMETLAB 2.0 (https://admetmesh.scbdd.com/) was utilized to assess the toxicity of the ligands [21, 22].

Molecular Docking

PyRx is a virtual screening software used for molecular docking and drug discovery, enabling the evaluation of ligand-protein interactions to predict binding affinities [14–23]. Molecular docking of the three ligands, Decan-1-ol and 2,3,4,6-Tetramethyl-D-Glucose against the 1EXT protein was performed using the PyRx virtual screening tool. The protein was uploaded as a macromolecule into the PyRx software. To prepare the protein for docking, the purified 1EXT protein was converted into the .pdbqt format.

The three ligands were obtained in .sdf format and were subjected to energy minimization using the universal force field. The torsions of each ligand were detected, and the energy-minimized ligands were subsequently converted into .pdbqt format using the OpenBabel feature of PyRx.

Grid dimensions of X=84.5986Å, Y=66.4871Å, and Z=67.5021 Å were selected for the docking process. Each ligand was docked independently against the 1EXT protein, where the ligands adopted nine different conformations to achieve the optimal binding conformation with the protein. The binding affinities were evaluated based on energy values, and the best docking conformation was identified by selecting the ligand with the least binding affinity score and zero root mean square deviation (RMSD) values [24].

Visualization of Docked Results

The docked structures from PyRx were visualized using the structure visualization tool BIOVIA discovery studio software. The best binding conformations were retrieved in .pdb format and viewed with BIOVIA Discovery Studio Visualizer. The non-bond interactions and the two-dimensional and three-dimensional models were investigated.

RESULTS

Protein Analysis

The Ramachandran plot is a graphical representation of the phi (φ) and psi (ψ) dihedral angles of amino acid residues present in the protein. It serves as a crucial tool for evaluating the stereochemical quality of a protein model. This analysis was performed using the Procheck (PDBsum) (Figure 2) and SAVES server (Figure 3**)**. In this analysis, the distribution of residues has been evaluated within favored, allowed, and disallowed regions of the Ramachandran plot. Additionally, G-factors were analyzed to assess the overall structural quality (Tables 1 and 2).

Table 1. Residue distributions.

Region	No. of Residues	Percentage
Most favored regions [A, B, L]	260	90.6%
Additional allowed regions [a, b, l, p]	27	9.4%
Generously allowed regions [~a, ~b, ~l, ~p]	0	0.0%
Disallowed regions [XX]	0	0.0%

Table 2. Special residues analysis.

Residue Type	No. of Residues
Non-glycine & Non-proline Residues	287
End-Residues (Excluding Glycine & Proline)	3
Glycine Residues (Triangles in Plot)	18
Proline Residues	10
Total Residues	318

Ramachandran Plot Analysis

The analysis indicates the following residue distributions in the Ramachandran plot.

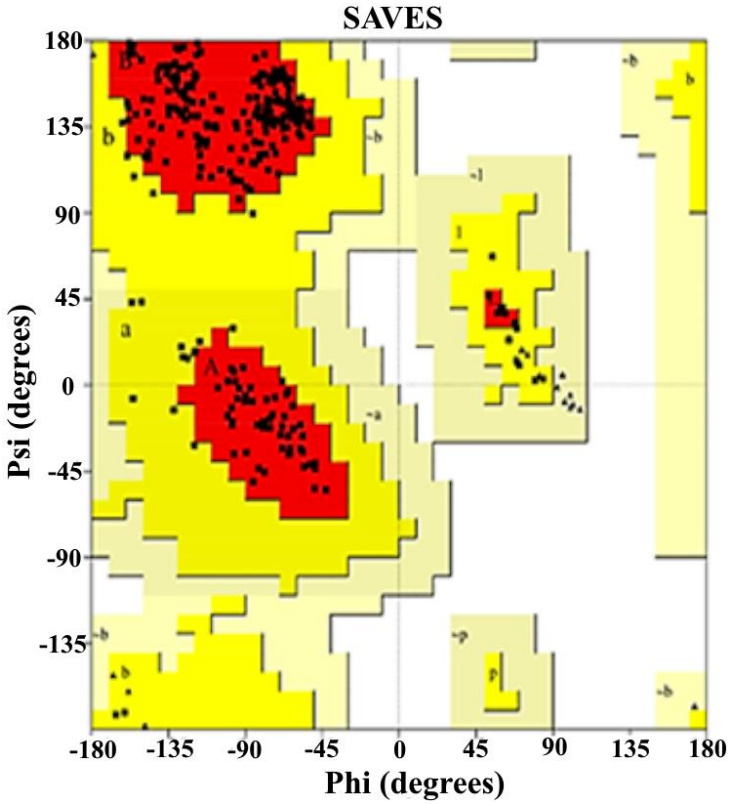

Figure 2. SAVES serves Ramachandran plot.

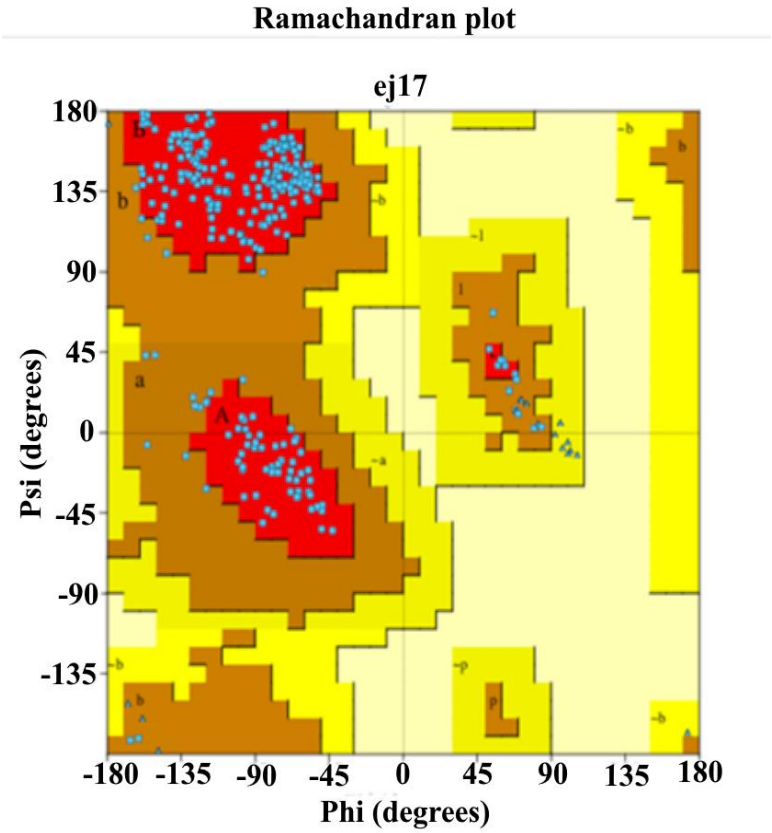

Figure 3. PDBSum generates Ramachandran plot.

A good-quality protein structure is expected to have >90% residues in the most favored regions based on an analysis of high-resolution protein structures. In this case, 90.6% of residues fall within the most favored regions, indicating that the model meets quality standards. Additionally, there are no residues in the disallowed regions, which further supports structural reliability.

G-Factor Analysis

The G-factor scores deliver how unusual the protein's structural is and these parameters are compared to standard protein structures (Table 3).

Table 3. G-factor analysis.

Dihedral Angle G-Factors	**Score**
Phi-Psi Distribution	–0.42
Chi1-Chi2 Distribution	0.17
Chi1 Only	0.16
Chi3 & Chi4	0.61
Omega	0.68
Average Dihedral Score	0.21
Phi-Psi Distribution	–0.42
Chi1-Chi2 Distribution	0.17
Chi1 Only	0.16
Main-Chain Covalent Forces G-Factors	
Main-Chain Bond Lengths	0.60
Main-Chain Bond Angles	0.20
Average Main-Chain Score	0.37
Main-Chain Bond Lengths	0.60

Overall Average G-Factor is 0.28. G-factor below –0.5 is considered unusual, and below –1.0 is highly unusual. Since all values are above –0.5, the structure is well-refined and does not show significant aberrations.

90.6% of residues are in the most favored regions, indicating a high-quality model. No residues are in disallowed regions, confirming good structural integrity. G-factor scores are within acceptable ranges, showing no significant conformational abnormalities.

Predicted secondary structure of 1EXT protein chain A includes 7 sheets, 7 beta hairpins, 4 beta bulges, 14 strands, 3 helices, 21 beta turns, 1 gamma turn and 12 disulphides according to PDBsum data as shown in Figure 4.

Phytochemical Selection and Pharmacological Screening

A total of 12 phytocompounds were retrieved from the Oshadi database (Table 4), along with their corresponding SID (Table 4). These compounds were subjected to pharmacokinetic screening using the SwissADME tool to assess their drug-likeness based on Lipinski's Rule of Five. Among the 12 compounds, phytocompounds which did not meet the selection criteria and were excluded. The remaining two phytocompounds Decan-1-ol (SID: 8174) and 2,3,4,6-Tetramethyl-D-glucose (SID: 12903171) exhibited high GI absorption and favorable bioavailability, making them suitable for molecular docking studies. The structures of Decan-1-ol (SID: 8174) and 2,3,4,6-Tetramethyl-D-glucose (SID: 12903171) are depicted in Figure 5.

Both Decan-1-ol and 2,3,4,6-Tetremethyl-D-Glucose meet the key Lipinski criteria, with molecular weights (MW) under 500 Da, low MLOGP values, and acceptable numbers of H-bond acceptors and donors. These properties suggest that the compounds are likely to have good oral bioavailability (Table 5).

Table 4. Phytocompounds retrieved from Oshadi database.

Phytocompound	SID	Phytocompound	SID
Decan-1-ol	8174	2,3,4,6-TETRAMETHYL-D-Glucose	12903171
1,3-Distearin	101269	Arbortristoside C	23955893
Glucomannan	24892726	Crocin	5281233
Crocin II	9940690	NSC606979	5459045
Nyctanthic acid	273516298	Kaempferol-3-rutinoside	5318767
Crocin-3	10461942	Nyctanthoside	95224501

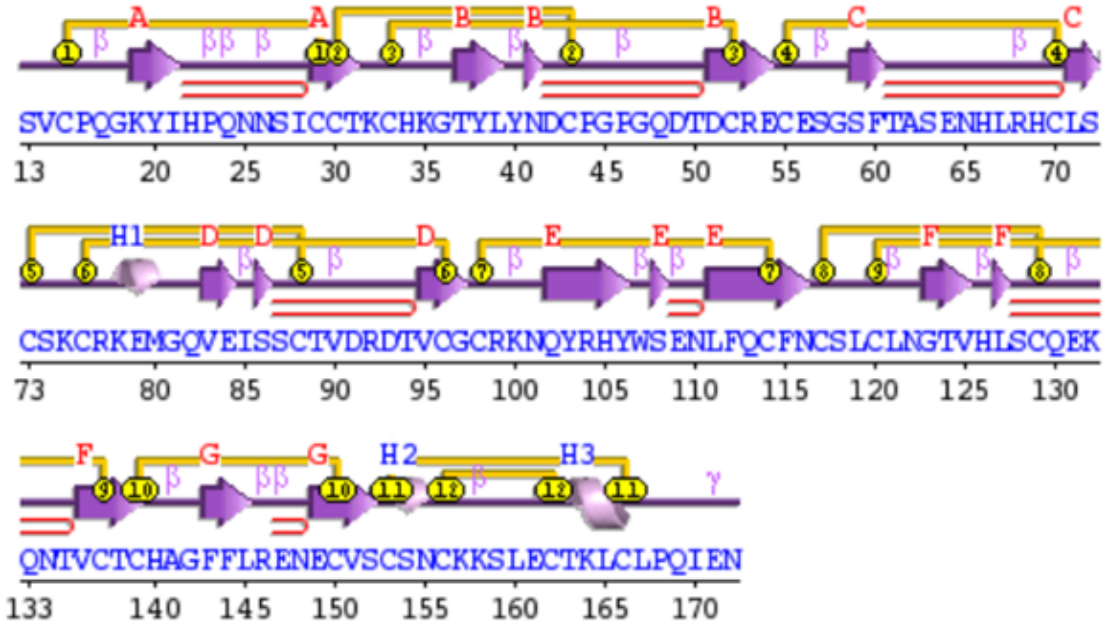

Figure 4. Secondary structure of protein 1EXT using PDBsum.

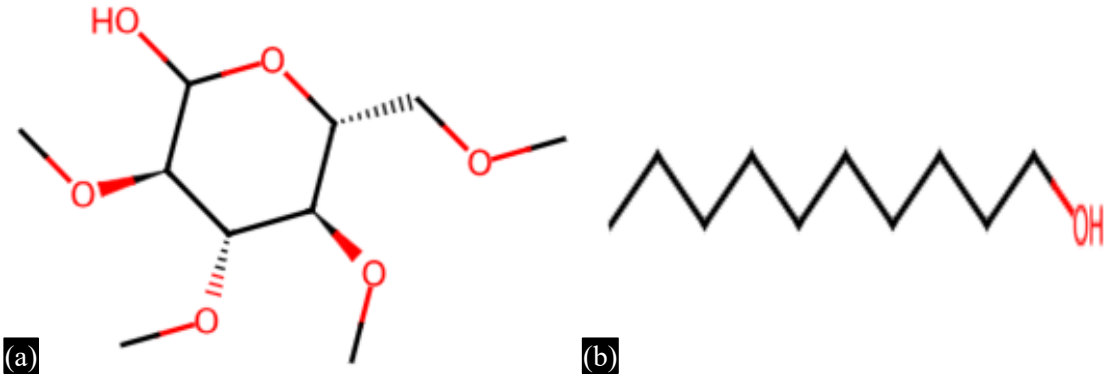

Figure 5. The 2D structures of Ligands. (a) 2,3,4,6-TETRAMETHYL-D-Glucose, (b) Decan-1-ol.

Both ligands show ideal fraction Csp3 values (1), indicating they are highly saturated, which is typically a desirable trait for drug-like molecules. Decan-1-ol has a higher number of rotatable bonds (8) compared to 2,3,4,6-Tetramethyl-D-Glucose (5), which may affect its flexibility and binding to the target (Table 6).

Based on the physicochemical and ADME properties two ligands (Decan-1-ol and 2,3,4,6-Tetramethyl-D-Glucose) exhibit high GI absorption and a bioavailability score of 0.55, indicating good

potential for systemic distribution. Decan-1-ol shows high BBB permeability, while 2,3,4,6-Tetramethyl-D-Glucose is more hydrophilic (Table 7).

Table 5. Data for the properties of Lipinski rule obtained using SwissADME.

Ligand	MW	MLOGP	H-Bond Acceptor	H-Bond Donor	MR
Decan-1-ol	158.28	2.84	1	1	51.35
2,3,4,6-TETRAMETHYL-D-Glucose	236.26	–1.45	6	1	54.66

Table 6. Physicochemical properties of the ligand molecules.

Ligand	Formula	Fraction Csp3	#Rotatable Bonds
Decan-1-ol	C10H22O	1	8
2,3,4,6-TETRAMETHYL-D-Glucose	C10H20O6	1	5

Table 7. ADME data obtained using SwissADME.

Ligand	GI Absorption	BBB Permeant	Pgp Substrate	Bioavailability Score	Silicos-IT LogSw
Decan-1-ol	High	Yes	No	0.55	–3.32
2,3,4,6-TETRAMETHYL-D-Glucose	High	No	No	0.55	–0.2

Toxicity Prediction

Toxicity prediction encompasses several critical components. Among these are skin sensitivity, carcinogenic potential, respiratory toxicity, AMES test results, acute oral toxicity in rats, FDAMDD, hERG blockers, H-HT, and drug-induced liver injury (DILI). These factors were all considered as outlined in Table 8.

Table 8. Toxicity analysis.

Ligand	hERG	H-HT	DILI	Ames	ROA	Carcinogenicity	Respiratory	Skin Sen
Decan-1-ol	0.089	0.017	0.038	0.007	0.048	0.074	0.285	0.916
2,3,4,6-TETRAMETHYL-D-Glucose	0.194	0.181	0.063	0.301	0.133	0.043	0.064	0.548

Molecular Docking Analysis

The molecular docking study using PyRx provided binding affinity values for the selected ligands, Decan-1-ol and 2,3,4,6-Tetramethyl-D-Glucose, against the 1EXT protein. The binding affinity values, as obtained from PyRx, are summarized in Table 9.

Table 9. Binding affinity of the ligands with protein.

Ligand	Binding Affinity
Decan-1-ol	–4.5
2,3,4,6-Tetramethyl-D-Glucose	–4.2

Visualization

The 2D and 3D models of the top five docked ligands with the best binding scores were generated and downloaded by utilizing BIOVIA Discovery Studio. The type of interactions, non-bond atoms, bond distances, and bond type were evaluated. The binding interactions of the ligands with the 1EXT protein were visualized using 2D and 3D interaction diagrams shown in Figures 6 and 7.

DISCUSSION

Rheumatoid arthritis (RA) is a long-lasting autoimmune disorder that is mainly marked by ongoing inflammation in the joints. The development of RA is significantly affected by the excessive production of pro-inflammatory cytokines, particularly Tumor Necrosis Factor-alpha (TNF-α), which is crucial in

facilitating inflammation and the activation of immune cells. The TNF receptors, TNFR1 and TNFR2, located on different cell types, act as the binding sites for TNF-α, initiating a series of inflammatory reactions. Consequently, focusing on these receptors presents a promising approach for the treatment of RA and the preservation of joint integrity [25, 26].

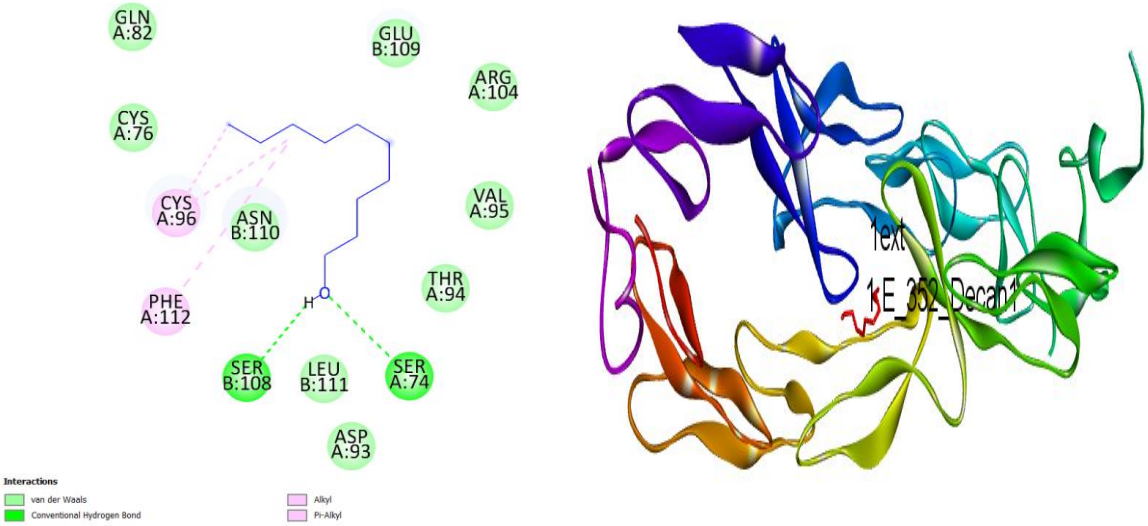

Figure 6. 2D and 3D interaction of Decan-1-ol with 1EXT protein.

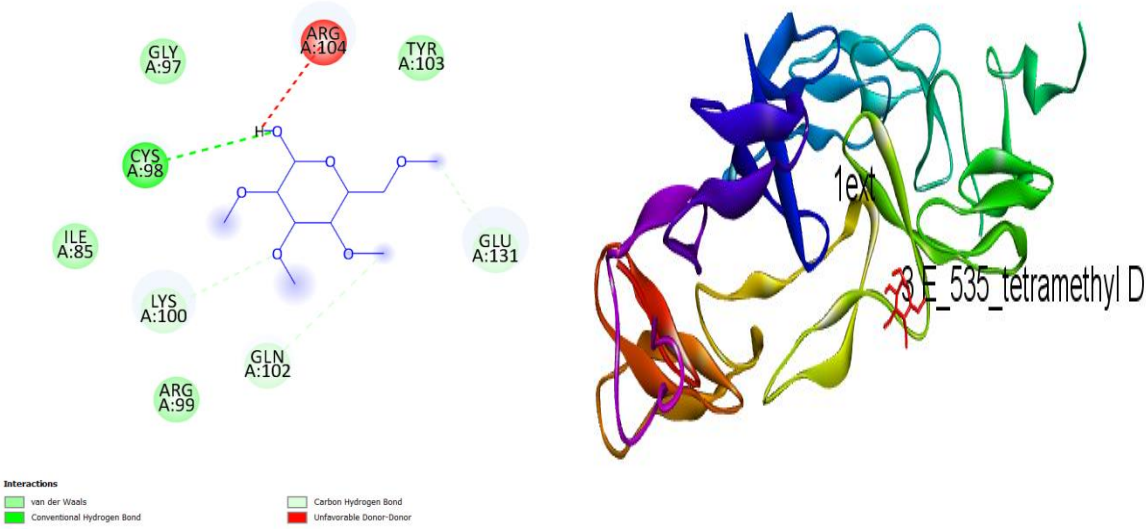

Figure 7. 2D and 3D Interaction of 2,3,4,6-Tetramethyl-D-Glucose with 1EXT protein.

This study examined the phytochemicals of *Nyctanthes arbor-tristis* for targeting the TNF receptor in arthritis with the help of molecular docking analysis. The findings reveal several promising insights regarding the interaction between selected compounds and the TNF receptor's extracellular domain.

The Ramachandran plot analysis of the TNF receptor (PDB ID: 1EXT) demonstrated excellent stereochemical quality, with 90.6% of residues in the most favored regions and no residues in disallowed regions. The overall G-factor of 0.28 indicates a well-refined structure suitable for molecular docking studies. The protein's secondary structure, comprising 7 sheets, 14 strands, and 3 helices, provides multiple potential binding sites for ligand interaction.

Among the twelve phytochemicals that were initially evaluated, Decan-1-ol and 2,3,4,6-Tetramethyl-D-glucose were identified as the most promising candidates due to their advantageous drug-like characteristics. Both substances comply with Lipinski's Rule of Five, which implies a likelihood of favorable oral bioavailability. The compounds exhibit high gastrointestinal absorption and bioavailability scores of 0.55, underscoring their potential as effective therapeutic agents. Importantly, Decan-1-ol's capacity to penetrate the blood–brain barrier (BBB) may provide additional therapeutic benefits; however, this characteristic necessitates careful evaluation of possible side effects.

The molecular docking results revealed moderate binding affinities for both compounds, with Decan-1-ol showing slightly stronger binding (–4.5 kcal/mol) compared to 2,3,4,6-Tetramethyl-D-glucose (–4.2 kcal/mol). While these binding energies are modest compared to some synthetic TNF inhibitors, they suggest potential biological activity needs further investigation. The binding interactions observed in the 2D and 3D models indicate specific molecular recognition between the ligands and the receptor's binding pocket.

Toxicity predictions using ADMET analysis showed favorable safety profiles for both compounds. The low probability scores for hERG inhibition, hepatotoxicity (DILI), and carcinogenicity are particularly encouraging. However, the relatively high skin sensitization score for Decan-1-ol (0.916) suggests caution may be needed regarding topical applications.

These findings align with traditional uses of *Nyctanthes arbor-tristis* in treating inflammatory conditions, as reported by Saxena et al. (1984) and more recently by Sharma et al. (2024) [9, 10]. The identification of specific molecular interactions between these phytochemicals and the TNF receptor provides a mechanistic basis for the plant's reported anti-inflammatory properties. The moderate binding affinities observed might explain the gentle but sustained anti-inflammatory effects often associated with traditional herbal medicines.

While the computational analysis provides promising initial results, several limitations should be acknowledged, like this study focused on the extracellular domain of the TNF receptor, and interactions with other domains may be relevant. Future research should include molecular dynamics simulations to better understand the stability of these interactions, in vitro studies to validate the predicted binding interactions, and investigation of potential synergistic effects between multiple phytochemicals.

The results of this study provide a foundation for further investigation of *Nyctanthes arbor-tristis* phytochemicals as potential therapeutic agents for inflammatory conditions, particularly rheumatoid arthritis. The combination of favorable drug-like properties and specific molecular interactions with the TNF receptor suggests these compounds may offer new opportunities for developing natural anti-inflammatory agents.

CONCLUSIONS

This computational study successfully identified two promising phytochemical compounds from *Nyctanthes arbor-tristis* – Decan-1-ol and 2,3,4,6-Tetramethyl-D-glucose – as potential modulators of TNF receptor activity. The molecular docking analysis revealed moderate binding affinities (–4.5 kcal/mol and –4.2 kcal/mol, respectively) between these compounds and the extracellular domain of the TNF receptor (1EXT), suggesting their potential therapeutic role in inflammatory conditions like rheumatoid arthritis.

These findings provide molecular-level support for the traditional use of *Nyctanthes arbor-tristis* in treating inflammatory conditions and offer new insights into the potential mechanisms of its anti-inflammatory properties. The identification of specific molecular interactions between these phytochemicals and the TNF receptor opens new avenues for the development of natural anti-inflammatory agents.

However, further research is necessary to validate these computational predictions. This should include in vitro binding studies, cellular assays to confirm TNF receptor modulation, and eventually, in vivo studies to evaluate therapeutic efficacy. Additionally, investigation of potential synergistic effects between these compounds and structure-activity relationship studies could lead to the development of more potent derivatives.

Acknowledgment

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List of Abbreviations

TNF: Tumor Necrosis Factor
RA: Rheumatoid Arthritis
SID: Substance Identifiers

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