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Exploring Phytochemicals from *Ricinus Communis* for Potential Therapeutic Applications in Rheumatoid Arthritis: An in-Silico Approach

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Abstract

Aim: *Rheumatoid arthritis (RA) is a long-term autoimmune condition characterized by the immune system mistakenly attacking the joints, leading to swelling, discomfort, and joint deformities. Current management strategies include anti-rheumatic drugs and biologics, which have limitations. This study aims to explore the therapeutic potential of Ricinus communis (castor bean plant) phytochemicals as plant-based therapies for autoimmune conditions, like RA.* ***Methods:*** *Phytochemicals from Ricinus communis were retrieved using the IMPPAT database, identifying 95 compounds. Their drug-like properties were evaluated using the SwissADME tool, resulting in the selection of seven compounds: Ricinine, Apigenin, Glycolic acid, Shikimic acid, Nicotinamide, threo-9, 10-Dihydroxystearic acid, and uric acid. Toxicity assessments were conducted using the protox tool. Molecular docking was performed with pyrx to evaluate interactions was achieved using BIOVIA.* ***Results:*** *This study revealed that Ricinus communis Phytochemicals demonstrated strong binding affinities with autoimmune pathway-related proteins 1A8M and 1TNF, indicating significant anti-inflammatory and immunomodulatory potential. These findings suggest their promise as plant-based therapeutic agents for RA.* ***Conclusion:*** *This research underscores the promising anti-inflammatory and immunomodulatory properties of phytochemicals derived from Ricinus communis. The identified compounds exhibit favorable drug-like and safety profiles, with significant binding to autoimmune pathway-related proteins. These findings provide a foundation for experimental studies and the development of plant-based therapies for autoimmune disorders, such as RA.*

Keywords: Rheumatoid arthritis, *Ricinus communis*, phytochemicals, autoimmune disorders, molecular docking, anti-inflammatory, immunomodulatory

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by persistent inflammatory processes that can damage joints as well as other organs, such as the heart, kidneys, lungs, digestive system, eye, skin, and nervous system [1]. While evidence suggests that RA existed in early Native American populations thousands of years ago, it is believed to have appeared in Europe and around the 17th century [2]. The disease has a variable clinical progression and an unpredictable prognosis. RA affects approximately 1–3% of the population and is more predisposition to RA has also been reported [3].

Tumor necrosis factor-alpha (TNF-alpha) is a multifunctional cytokine protein that plays a central role in cell differentiation, proliferation,

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and survival. TNF-alpha is a critical component of the immune system, mediating inflammatory and immune response against pathogens, such as viruses, bacteria, parasites, and tumors [4]. It is essential for various phytochemicals processes, including embryonic development, innate and adaptive immunity, and cellular homeostasis. TNF-alpha is particularly significant in the host's defense mechanisms against pathogens [5].

Plants have long been a source of important therapeutic agents. *Ricinus Communis* has been used in traditional medicine as a natural remedy for variety of aliments worldwide. The plant is rich in phytochemicals, including alkaloids, terpenes and phenolic compounds, which have demonstrated anticancer, antimicrobial, and immunological properties [6]. The plant kingdom provides an abundant source of bioactive organic compounds, many of which have medicinal applications. In traditional medicine, *Ricinus Communis* also known as the castor plant, is recognized for its potential to treat numerous diseases and disorders [7].

The plants hold significant medical value, traditionally being used as laxative, purgative, fertilizer, and fungicide. Additionally, it exhibits a wide range of pharmacological activities, including antioxidant, antihistaminic, antinociceptive, antiasthamatic, antiulcer, immunomodulatory, antidiabetic, hepatoprotective, antifertility, anti-inflammatory, antimicrobial, center nervous system stimulant, and lipolytic properties. These activities are attributed to its rich phytochemical composition, including flavonoids, saponins, glycosides, alkaloids, and steroids [7].

To obtain a potent natural drug targeting the desired protein, a computer-aided drug design (CADD) or an in-Silico molecular docking analysis is a low-cost and rapid solution. It is widely acknowledged that medication development and manufacture are time-consuming and energy intensive operations. As a result, an increase in efforts is being made to adapt computing power to the combined chemical and biological domain to expedite the drug development process. Computer-aided or in-Silico architecture is used in the biomedical arena to speed up and promote hit detection, hit-to-lead collection, optimize the profile of absorption, distribution, metabolism, excretion, and toxicity, and prevent security problems. Molecular docking examines how tiny molecules known as ligands interact with the target macromolecule's active binding pocket (receptor proteins). In addition to generating binding energies, the position of ligand in the enzyme binding site can be visualized in these docking studies. It may be useful for the development and understanding of the binding nature of potential drug candidates [8].

MATERIALS AND METHODS

Retrieval of Phytochemicals

Plant *Ricinus communis,* phytochemicals of this plant retrieved from IMPPAT database. A total of 95 phytochemicals were selected based on their potential relevance in treatment of autoimmune disorder, like rheumatism. The compounds were then subjected to further analysis, including phytochemicals properties screening and toxicity prediction. To identify those with promising drug-like characteristics for molecular docking and therapeutic evolution.

ADME Screening

Conduct ADME screening for *Ricinus communis* phytochemicals using SwissADME to evaluate their pharmacokinetic properties. Focus on parameters, like GI absorption, Lipinski's rule compliance, bioavailability score, solubility (ESOL), BBB permeability, and synthetic accessibility.

Toxicity Screening

Perform toxicity analysis using tools like Protox to assess the safety of the selected phytochemicals. Analyze LD50 values, organ-specific toxicities, carcinogenicity, mutagenicity, and immunotoxicity to identify safe and effective candidates for therapeutic safe and effective candidates for therapeutic applications.

Retrieval of Proteins

Retrieval of structure of the two proteins, the structure of tumor factor-alpha at 2.6 angstroms resolution. Implication for receptor binding (1A8M) and the structure of tumor factor-alpha at 2.6 angstroms resolution, Implication for receptor binding (1TNF) from the RCSB PDB (https://www.rcsb.org/). The protein data bank was the first open-access digital repository created to serve the fields of biology and medicine.

Target Protein

The 1A8M structure represents the R31D mutant of tumor necrosis factor alpha (TNF-α), classified as a lymphokine involved in inflammation and immune response. Resolved through x-ray diffraction at a 2.30 Å resolution, it originates from Homo sapiens and was expressed in Escherichia coli. Its structural details, including mutation analysis, are critical for designing therapeutics targeting autoimmune and inflammatory disorders. The 1TNF structure depicts the native form of TNF-α, a key lymphokine mediating inflammation and immune regulation. Determined via X-ray diffraction at a 2.60 Å resolution, it originates from Homo sapiens without mutations. Its structural insights are fundamental for understanding receptor interactions and developing anti-inflammatory therapeutics.

Structure Validation

The validated structure of 1A8M and 1TNF are crucial for ensuring accuracy in molecular docking studies. Their resolution and quality parameters, such as R-value and Ramachandran plot analysis, confirm their reliability for simulating protein-ligand interactions. Utilizing experimentally resolved structures ensures precise binding affinity predictions, aiding in the identification of potential therapeutic candidates. Computational docking leverages these validated structures to predict molecular mechanisms, expediting drug discovery for autoimmune and inflammatory disorder.

Molecular Docking

Molecular docking predicts the interaction between target proteins and ligands to evaluate binding affinities, aiding drug discovery. Using PyRx, a user-friendly tool, docking is performed by selecting protein and ligand structures, preparing them, and simulating interactions. It helps identify promising compounds based on their binding scores and poses accelerating therapeutic development.

Molecular Visualization

Molecular visualization helps analyze protein-ligand interactions, providing insights into binding mechanisms and structure stability. Using BIOVIA, 3D and 2D visualization are created to examine docking results, allowing for the interpretation of interactions at atomic and molecules levels. This process is essential for understanding drug efficacy and optimizing lead compounds in drug discovery.

RESULT

Retrieval of Phytochemicals

The 3D structures of three phytochemicals Apigenin (5280443)**,** Shikimic acid (8742), and Uric acid (1175) were retrieved from the BIOVIA Discovery Studio for precise modelling and docking studies (Figure 1). These structures were optimized for interaction analysis with target proteins. This ensured accurate molecular docking and protein-ligand interaction insights.

ADME Screening

Seven phytochemicals from *Ricinus communis* were analyzed for their drug-likeness and toxicity. The selected compounds include ricinine, Apigenin, glycolic acid, Shikimic acid, nicotinamide, three-9-10-dihydroxystearic acid, and uric acid. Key parameters, such as molecular weight (MW), H-bonding acceptors and donor, and GI absorption were evaluated using swissADME, all compounds demonstrated high gastrointestinal absorption and passed Lipinski rules, and no pan assay interference compounds (PAINS) were detected ensuring their suitability for further molecular docking and interactions studies (Tables 1 and 2).

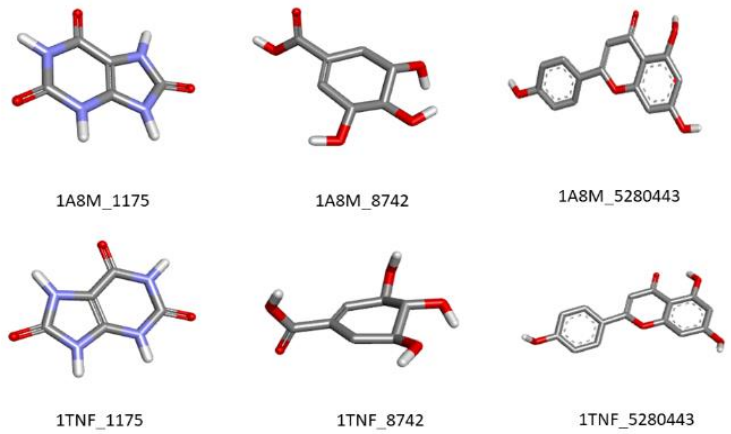

Figure 1. Ligands 3D structure.

Table 1. Physicochemical probability of phytochemicals.

Compound	PubChem ID	Formula	Molecular Weight	MR	TPSA	#H-Bond Donors	#H-Bond Acceptors
Ricinine	10666	C8H8N2O2	164.16	43.17	55.02	0	3
Apigenin	5280443	C15H10O5	270.24	73.99	90.9	3	5
Glycolic acid	757	C2H4O3	76.05	14.66	57.53	2	3
Shikimic acid	8742	C7H10O5	174.15	38.43	97.99	4	5
Nicotinamide	936	C6H6N2O	122.12	32.33	55.98	1	2
threo-9, 10-Dihydroxystearic acid	12235228	C18H36O4	316.48	92.74	77.76	3	4
Uric acid	1175	C5H4N4O3	168.11	40.16	114.37	4	3

Table 2. Drug likeliness of phytochemicals.

Compound	Solubility	GI Absorption	BBB Permeant	Lipinski	PAINS	Bioavailability Score	Synthetic Accessibility
Ricinine	Very soluble	High	No	0	0	0.55	1.9
Apigenin	Soluble	High	No	0	0	0.55	2.96
Glycolic acid	Highly soluble	High	No	0	0	0.85	1
Shikimic acid	Highly soluble	High	No	0	0	0.56	3.77
Nicotinamide	Very soluble	High	No	0	0	0.55	1
threo-9, 10-Dihydroxystearic acid	Soluble	High	No	0	0	0.56	3.46
Uric acid	Very soluble	High	No	0	0	0.55	1.8

Toxicity Screening

The toxicity profiles of the selected *Ricinus communis* phytochemicals were evaluated using ProTox, which predicts potential toxic effects based on LD50 values and toxicity classes. Compounds, like Ricinine (1000 mg/kg) and Apigenin (2500 mg/kg), were classified in toxicity classes 4 and 5, respectively, indicating low toxicity. Various toxicity parameters, such as Hepatotoxicity, Nephrotoxicity, Carcinogenicity, and Nutritional toxicity were assessed, showing that most compounds exhibit minimal toxicity. Shikimic acid, with the highest LD50 (9000 mg/kg) demonstrated the most balanced toxicity profile. This analysis aids in identifying safe and effective phytochemicals for further drug development (Table 3).

Table 3. Toxicity screening.

Compounds	LD50	LD Class	Toxicity Class			
			Hepatotoxicity	Nephrotoxicity	Carcinogenicity	Nutritional Toxicity
Ricinine	1000 mg/kg	4	Inactive – 0.71	Inactive – 0.63	Inactive – 0.60	Inactivev – 0.66
Apigenin	2500 mg/kg	5	Inactive – 0.68	Active – 0.60	Inactive – 0.62	inActive – 0.55
Glycolic acid	1938 mg/kg	4	Inactive – 0.96	Active – 0.50	Inactive – 0.86	Inactive – 0.71
Shikimic acid	9000 mg/kg	6	Inactive – 0.70	Active – 0.64	Inactive – 0.66	Active – 0.64
Nicotinamide	2500 mg/kg	5	active – 0.54	inActive – 0.70	Inactive – 0.92	inActive – 0.54
threo-9, 10-Dihydroxystearic acid	3400 mg/kg	5	Inactive – 0.70	Active – 0.59	Inactive – 0.71	Inactive – 0.78
Uric acid	500 mg/kg	4	Inactive – 0.71	inActive – 0.54	Inactive – 0.55	Inactive – 0.91

Retrieval of Protein

The proteins 1TNF and 1A8M both crucial in the study of autoimmune disorder, like Rheumatism, were purified using BIOVIA software. After purification, the structures were saved as 3D PDB files for further computational analysis (Figures 2 and 3). These purified structures allow for accurate molecular docking and interactions studies, which are integral to understanding the binding affinity of selected phytochemicals from *Ricinus communis.*

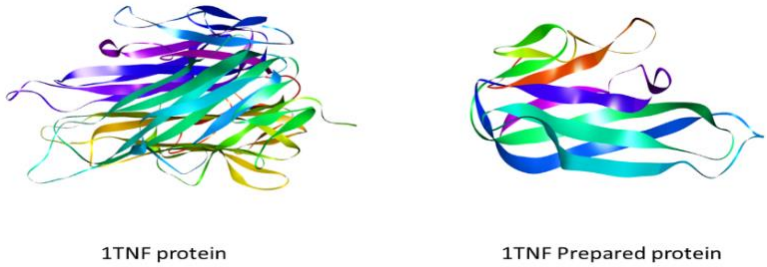

Figure 2. 3D structure of the 1TNF prepared protein.

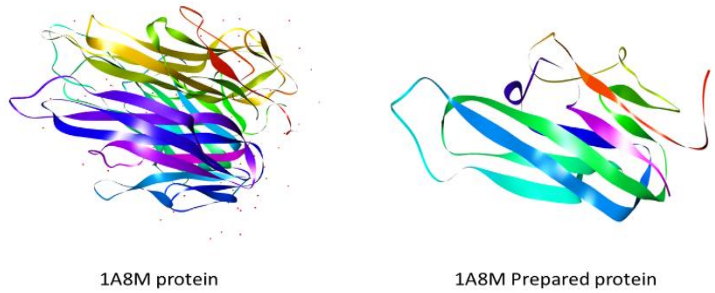

Figure 3. 3D structure of the 1A8M prepared protein.

Target Ligand Selection

The drug name is a FDA-approved agent for the treatment of disease. The standard structural file of these compounds was procured from the PubChem database, and the structure was visualized with DS biovia discovery studio visualizer. The drug name was prepared by adding the universal force field (_uff) and the ligand structure files were converted to PDBQT format using pyrx for docking simulations (Table 4).

Table 4. Drug targeted phytochemicals.

S.N.	Phytochemicals	PubChem id
1	Apigenin	5280443
2	Shikimic acid	8742
3	Uric acid	1175

Molecular Docking

The docking study focused on the evaluation of binding affinities between a suite the protein target 8HQ1, providing critical insights for potential drug discovery. Binding affinities were measured in kilocalories per mole (Kcal/mol), with lower values indicative of stronger and more energetically favorable ligand-protein interactions. A range of affinities was observed from -5.3 to -10.7 kcal/mol (Tables 5 and 6).

Table 5. Molecular docking of phytochemicals with 1TNF protein.

Phytochemicals	Binding Affinity with 1TNF in kcal/mol
Apigenin	–6.7
Shikimic acid	–5.5
Uric acid	–5.8

Table 6. Molecular docking of phytochemicals with 8HQ1 protein.

Phytochemicals	Binding Affinity with 8HQ1 in kcal/mol
Apigenin	–6.6
Shikimic acid	–5.7
Uric acid	–6.4

Molecular Visualization

The docking interactions between selected phytochemicals (uric acid, Shikimic acid and Apigenin) and the target protein 1TNF and 1A8M are visualized. The phytochemicals are represented in red, interactions with the active protein sites (green). The surface of the proteins indicates the hydrophobic (white/green) and hydrophilic (purple) regions, illustrating the binding conformations of each compound (Figure 4). These interactions provide insights into the binding affinities and potential inhibitory effects of the phytochemicals on the target proteins, aiding in the development of therapeutic strategies for immune disorders, like rheumatism.

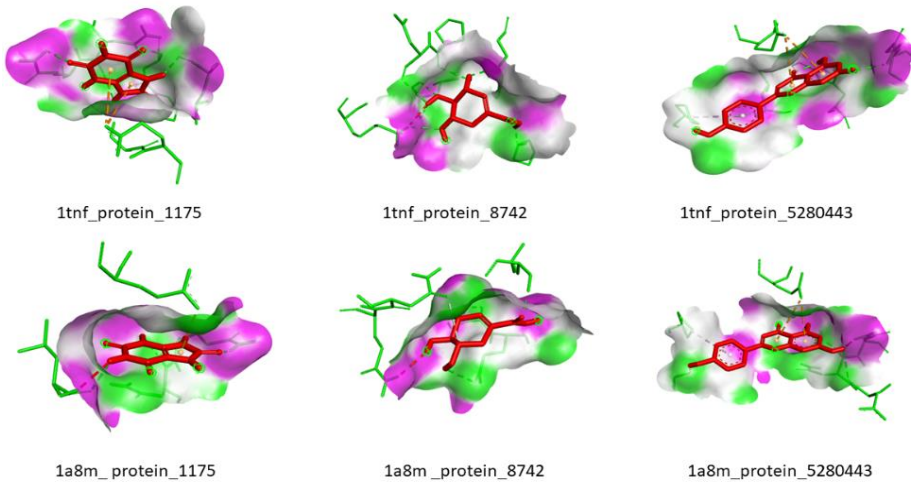

Figure 4. Visualization of molecular interactions of phytochemicals with 1TNF and 1A8M proteins of 3D structures.

The 2D interactions diagrams illustrate the binding interactions between the phytochemicals (uric acid, Shikimic acid and Apigenin) and the protein 1TNF and 1A8M. The green dashed lines represent hydrogen bonds, while the red lines indicate unfavorable donor-acceptor interactions. The key amino acids participating in the interactions are emphasized, with their side chains displayed surrounding the ligand (Figure 5). These diagrams provide a clear visualization of the molecular interactions, including, hydrogen bonding and hydrophobic interactions, crucial for understanding the binding affinity and potential therapeutic efficacy of these phytochemicals.

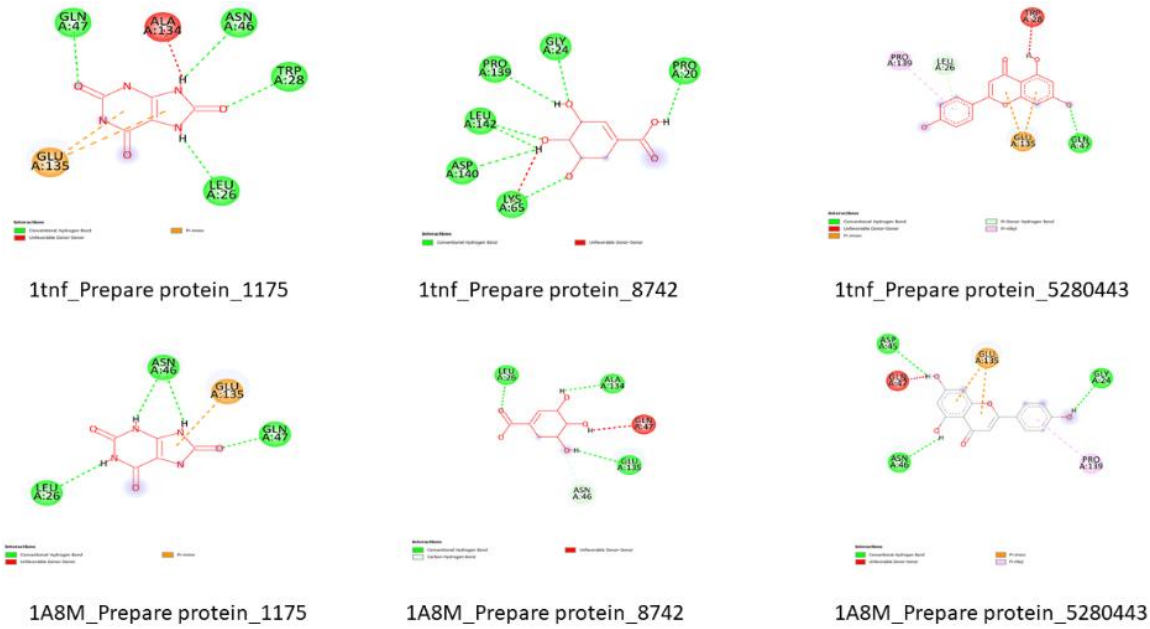

Figure 5. 2D interactions diagrams of phytochemicals with target proteins ITNF and 1A8M.

Ramachandran Plot

In my research project on the castor bean plant (*Ricinus communis*), I analyzed the structure quality of two proteins, 1TNF and 1A8M, using Ramachandran plots obtained from the SAVES sever (Figures 6 and 7). For the 1TNF protein, 65.1% of residues are in the most favored regions, 27.9% in additional allowed region, 3.9% in generously allowed regions, and 3.1% is disallowed regions, with an ERRAT score of 75. For the 1A8M protein, 57.4% of residues are in the most favored regions, 37.2% in additional allowed regions, 2.3% in generously allowed regions, and 3.1% in disallowed regions, with an ERRAT score of 77.083 (Table 7). These results provide insights into the structural stability and quality of the protein models, contributing to the assessment of their suitability for further molecular docking studies.

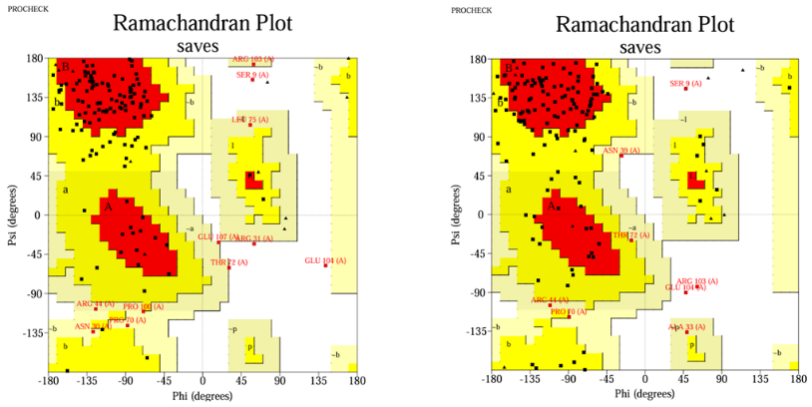

Figure 6. 1TNF Ramachandran plot. **Figure 7**. 1A8M Ramachandran plot.

Table 7. Ramachandra plot.

Ramachandran Plot regions	1TNF	1A8M
Residues in most favoured regions	65.1%	57.4%
Residues in additional allowed regions	27.9%	37.2%
Residues in generously allowed regions	3.9%	2.3%
Residues in disallowed regions	3.1%	3.1%

DISCUSSION

The study focuses on the identification of potential therapeutic phytochemicals (Figure 8) from *Ricinus communis* (Caster bean plant) for targeting autoimmune and inflammatory disease. Chronic inflammation is a hallmark of autoimmune disorders, like RA, is primarily driven by cytokines, including TNF-α. TNF-α plays a critical role in inflammation and immune regulation, making it a vital target for therapeutic intervention. Two THF- α protein structures, 1A8M (R31D) and 1TNF (native, were retrieved from the protein data bank (PDB) for this purpose. These structures, validation using Ramachandran plot and other quality metrics, provided a reliable framework for molecular docking studies, ensuring accurate simulation of protein-ligand interactions.

Ricinus communis, a renowned medicinal plant, has been extensively researched for its pharmacological benefits. Traditionally used in folk medicine, it exhibits anti-inflammatory, antioxidant, and antimicrobial activates. The phytochemicals profile of *Ricinus communis* was compiled from the IMMPAT database, yielding 95 compounds for initial screening. SwissADME was used to perform ADME (Absorption, Distribution, metabolism, and excretion) analysis on these compounds. This step ensured the selection of drug-like molecules based on parameters, such as gastrointestinal absorption, Lipinski's rule of five, and bioavailability scores. Seven phytochemicals, including ricinine, Apigenin, glycolic acid, Shikimic acid, nicotinamide, thero-9, 10-dihydroxystearic acid and uric acid were selected for further study based on favorable ADME profiles.

Figure 8. *Ricinus communis*, commonly referred to as the castor bean plant.

Toxicity analysis was performed using the protox tool, which provides insights into potential adverse effects, like hepatotoxicity, nephrotoxicity, and carcinogenicity. The selected compounds exhibited low toxicity, with Shikimic acid showing the highest LD50 value (9000mg/kg) least toxic profile. These finding reinforced their suitability for therapeutic applications. The protein was prepared and purified using BIOVIA Discovery Studio to enhance their compatibility with the selected phytochemicals for docking studies.

PyRx was utilized for molecular docking to assess the binding affinities of the chosen compounds with the target proteins. The docking results identified three top-preforming phytochemicals Apigenin, Shikimic acid, and uric acid based on their binding affinities and RMSD values. For the 1TNF protein, the binding affinities were –6.7 kcal/mol (Apigenin), –5.5 kcal/mol (Shikimic acid), and –5.8 kcal/mol (uric acid), similarly for, 1A8M, the binding affinities were –6.6 kcal/mol

(Apigenin), –5.7 kcal/mol (Shikimic acid), and –6.4 kcal/mol (uric acid). These finding suggest that the ligands from robust and stable interactions with the target's protein.

Apigenin, a flavonoid, demonstrated the highest binding affinity and is well-documented for its anti-inflammatory and antioxidant properties, which align with its role in modulating TNF-activity. Shikimic acid, a precursor of antiviral drugs, also showed promising results, highlighting its potential as an anti-inflammatory agent. Uric acid though primarily associated with metabolic functions, displayed moderate binding affinities, suggesting its role in modulating inflammatory pathways. The combined ADME, toxicity, and docking results position these phytochemicals as strong candidates for further experimental validation in the development of therapeutics for autoimmune and inflammatory diseases.

CONCLUSIONS

This study provides compelling evidence for the therapeutic potential of phytochemicals derived from *Ricinus communis* in the management of RA, a chronic inflammatory disorder characterized by the immune systems misguided attack on the joint tissues. Through a comprehensive analysis, we identified seven bioactive compounds with promising drug-like properties, focusing on their capacity to modulate autoimmune pathways. The selected phytochemicals – Ricinine, Apigenin, Glycolic acid, Shikimic acid, Nicotinamide, threo-9, 10-Dihydroxystearis acid, and Uric-demonstration favorable physicochemical characteristics and a robust safety profile, as confirmed by toxicity assessments using the Protox tool.

Furthermore, our molecular docking revealed that Apigenin, Shikimic acid, and Uric acid exhibited high binding affinities with the target protein 1TNF (binding energies of –6.7, –5.5, and –5.8 kcal/ mol, respectively) and 8HQ1 (binding energies of –6.6, –5.7, and –6.4 kcal/ mol, respectively). These results emphasize the potential of these compounds as potent inhibitors in inflammatory pathways. Showcasing their promise as leading options for developing plant-based treatments. This research not only enriches the understanding of the pharmacological benefits of *Ricinus communis* but also paves the way for future experimental validations. By leveraging the rich phytochemicals diversity of this plant, we may unlock novel strategies for treating autoimmune disorders, ultimately contributing to safer and more effective therapeutic options.

List of abbreviations

RA	Rheumatoid arthritis
ADME	Absorption, distribution, meta-bolism, excretion
TNF	Tumor necrosis factor
CADD	Computer aided drug design
IMPPAT	Indian Medicinal Plant, Phytochemicals and Therapeutics
GI	Gastrointestinal
LD50	Lethal dose

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