STM JOURNALS

International Journal of
Bioinformatics and Computational Biology

ISSN: 2583-9977
Volume 3, Issue 1, 2025
January—June
DOI (Journal): 10.37591/IJBCB

https://journals.stmjournals.com/ijbcb

Review IJBCB

Targeting PTPN22 in Arthritis: Molecular Docking and Pharmacokinetic Evaluation of *Artemisia vestita* Compounds

Shweta V. Bhat*

Abstract

Rheumatoid arthritis (RA) is a long-term autoimmune condition characterized by inflammation of the synovial membrane, commonly resulting in swelling, pain, stiffness, and overall fatigue. Protein tyrosine phosphatase non-receptor type 22 (PTPN22) has been identified as a risk factor linked to various autoimmune diseases, including RA. In the PTPN22 gene, two missense Single nucleotide polymorphisms (SNPs) are associated with autoimmune conditions. The R620W (C1858T, rs247660) variant in exon 14 has been shown to elevate the negative regulation of B and T cell activation. On the other hand, the R263Q (G788A, rs33396649) variant in exon 10 affects enzyme activity by altering a key amino acid. This study explores the potential of the phytochemical compounds from Artemisia vestita, a folklore medicinal plant with anti-inflammatory and antipyretic properties in the treatment of RA using computational tools. PyRx, a virtual screening software was employed to carry out the molecular docking stimulations. The compounds from A. vestita which demonstrated the most favorable binding with PTPN22 were Vulgarin, Thujyl alcohol, iso-3-Thujyl acetate, (+)-alpha-Thujone and Verbenone. These compounds were chosen for further in-silico analysis and were evaluated for drug-like properties based on ADMET parameters, Lipinski's rule of five and five physiochemical parameters: Bioavailability score, GI absorption, PAINS and Brenk alerts and solubility. The compound Vulgarin exhibited the best affinity toward PTPN22. Hence, the molecular interaction between PTPN22 and Vulgarin was visualized in DS BIOVIA Discovery Studio Visualizer.

Keywords: Rheumatoid arthritis, *Artemisia vestita*, protein tyrosine phosphatase non-receptor type 22(PTPN22), molecular docking, in silico analysis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease primarily affecting the joints and the soft tissues [1]. RA affects 0.5%–1% of the population globally [2]. Studies have revealed that between 1990 and 2019, the cases of RA rose from 5,67,462.89 to 10,74,390.80 and as of 2020, a 14.1% increase in the global incidence rate of arthritis was observed [3]. T cells and CD19+ B cells could contribute to bone damage in RA by facilitating inflammatory immune response [4]. While the exact cause of RA remains unknown, it is believed that genetic, environmental and immunological factors are involved [5]. The key inflammatory mediators for RA include tumor necrosis factor (TNF)-α and interleukin (IL)-6, which play a significant role in enhancing inflammatory immune response [5]. The common clinical manifestations of RA include inflammation of the joints, which lead to pain, stiffness and in

***Author for Correspondence**
Shweta V. Bhat
E-mail: shwetabhat4228@gmail.com

Student, Department of Bioinformatics, BioNome, Bengaluru, Karnataka, India

Received Date: December 27, 2024
Accepted Date: January 09, 2025
Published Date: January 30, 2025

Citation: Shweta V. Bhat. Targeting PTPN22 in Arthritis: Molecular Docking and Pharmacokinetic Evaluation of *Artemisia vestita* Compounds. International Journal of Bioinformatics and Computational Biology. 2025; 3(1): 20–31p.
DOI: https://doi.org/10.37591/IJBCB.v03i01.196140

some cases, deformities [5]. In about 40% of affected individuals, the extra-articular organs like the lungs, heart and other systems are also impacted, declining the overall health and life expectancy of the individual [6]. The disease is believed to advance in four stages: triggering, maturation, targeting and fulminant [6]. Certain factors like age, obesity, mucosal inflammation and viral infections increase the chances of RA [6]. The current treatment for RA focuses on the use of Disease-Modifying Anti-Rheumatic Drugs (DMARDs, antibiotics, anti-metabolite hormones and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [7, 8]. Developments made in targeted therapies have improved the result of treatments, helping many individuals attain remission [1]. Regardless of these developments, many patients still do not respond positively to current therapies. This stresses the importance of further research on alternative treatment options like natural therapies and a better understanding of the mechanisms behind the pathogenesis of RA [1].

A gene which has been identified as a significant susceptibility factor to RA is the Protein tyrosine phosphatase non-receptor type 22 (PTPN22) [9]. A study conducted by Pasha et al. (2023) revealed that the PTPN22 mutation (C1858T; rs2476601) leads to a substitution of R620 with W620 [10]. It was found that this change has a significant impact on the confirmation of key functional moieties in the mutant protein leading to weak binding of W620 with the receptor, SRC kinase [10]. The improper interaction and binding provided compelling evidence for the possibility of inadequate inhibition of T cell activation, which may explain the increased autoimmunity observed in RA patients [11].

Herbal treatments for RA have gained popularity due to their potential anti-inflammatory, pain-relieving, and antioxidant properties. Herbal therapies are often believed to result in fewer side effects as compared to conventional treatments used for RA and are also more cost-efficient. Several studies emphasized the effectiveness of certain herbs and suggested that they can act as complementary therapies in addition to standard treatments. For example, a study conducted by Mittal et al. (2024) suggested that herbs like Turmeric, Ginger, and Boswellia serrata had potential anti-inflammatory properties [12]. Despite the promising results, the author acknowledges that more rigorous clinical trials are necessary to assess the safety of these herbs. Another study proposed that pomegranate extract and chamomile potentially decreased self-reported pain in treatment groups [13]. Despite providing valuable insights, there was a significant reporting bias in the study which may have affected the accuracy of the results.

The genus *Artemisia,* which belongs to the Asteraceae family, is renowned for its therapeutic value [14]. It has gained popularity due to its diverse phytochemical profile and medicinal benefits [14, 15]. *Artemisia vesitia (A. vestita)*, commonly known as “Kubsha” or “Russian wormwood” is a folklore medicinal plant which belongs to the genus *Artemisia* and the Asteraceae family, well known for its therapeutic properties [16]. *A. vesitita* is a highly valuable traditional medicinal plant with inflammation-reducing, antipyretic, tumor-suppressing and antibacterial properties [16]. *A. vestita* is traditionally used in China and Tibet to treat inflammatory disease like RA [17]. A study reported that over 202 bioactive compounds including terpenoids, flavonoids, alkaloids, acetylenes, tannins, carotenoids, and coumarins were found in *A. vestita* which accounts for its pharmacological properties [16]. However, the author acknowledges that despite showing promising therapeutic potential, more thorough studies are necessary to better understand the active constituents, pharmaceutical standardization, and mode of action and sustainable conservation of *A. vestita* to evaluate its benefits [16]. Moreover, the study also concluded that many promising reports indicating the therapeutic benefits of *A. vestita* are fragmentary and show different results, which stresses the need for more comprehensive research to evaluate its medicinal properties [16]. While the medicinal properties of *A. vestita* seem promising, more in-depth research is needed to understand its efficacy and safety in treating RA.

This study aims to evaluate the pharmacological properties of the phytochemical compounds from *A. vestita* using computational tools and techniques to assess whether they can be considered suitable for the treatment of RA. The major computational method employed in this study is molecular docking

(MD). MD is a method used in Computer-Aided Drug Design (CADD) which determines the binding affinity of a ligand to a target protein [18, 19]. MD helps in understanding molecular activity, testing the therapeutic potential of the compound and identifying effective ligands for the receptor protein [19]. MD is a fast and simple technique which also helps in determining protein-ligand interactions and the conformations of the interactions [20]. Computational methods are advantageous as they help in reducing the time and expenses that are otherwise required during experimental methods [21]. In this study, the compounds are also screened for drug-like properties on the basis of five physiochemical criteria: Bioavailability score, Gastrointestinal (GI) absorption, PAINS and Brenk alerts and solubility, Lipinski's rule of five and Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) parameters. The 2D and 3D structure of the interactions between the best performing phytocompound of *A. vestita* and PTPN22 were also visualized using Dassault Systems (DS) BIOVIA discovery studio visualizer, a visualization tool that depicts the interactions between the ligand and the protein, which further helps in understanding the stability of the protein-ligand complex [22].

This study makes a significant contribution to drug discovery for RA treatment by identifying the compounds of *A. vestita* with the highest impact on the target protein PTPN22. The study also evaluates the physiochemical and toxicity profile of the most promising compounds, which paves the way for the development of more efficient targeted therapies and further clinical assessment.

METHODS

Retrieval of Ligands

The Indian Medicinal Plants, Phytochemistry and Therapeutics (IIMPAT) database was used to retrieve the ligands of *A. vestita* [23]. The canonical smiles of the ligands were documented. After identifying the 11 most promising ligands, their structures were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in the SDF format for further analysis [24].

Retrieval of Proteins

The structure of the protein PTPN22 with PDB ID 3OLR was obtained from the Protein Data Bank (PDB) database (https://www.rcsb.org/structure/3OLR) [25]. The protein was then downloaded in the PDB format. The protein has a resolution of 2.50 Å and was derived using the X-ray diffraction technique.

Protein Purification

Prior to docking, the protein PTPN22 was purified using the following procedure: First, water molecules were entirely removed as the free energy of the water molecule and the structure crystallographic structure of the protein did not match, and this can affect the docking scores. To facilitate better binding with chosen ligands, any ligands already bound to the protein were removed. The protein structure was further simplified by retaining only the A chain, while deleting the remaining chains. To refine the structure even more, polar hydrogen atoms were added to it. The entire purification process was performed using DS Biovia Discovery Studio visualizer [26].

Pharmacological Analysis

SwissADME (http://www.swissadme.ch/) was used to analyze the physiochemical properties of the selected ligands [27]. The ligands were screened based on Bioavailability score, GI absorption, PAINS and Brenk alerts and solubility. Following this, the ligands were evaluated according to the Lipinski rule of five. The toxicity profiles of the ligands were then assessed using ADMETlab 2.0 (https://admetmesh.scbdd.com/) [28].

Molecular Docking

Python Prescription (PyRx) is virtual screening software which was used to assess the binding affinities of the selected compounds against the 3OLR protein [29]. The purified version of PTPN22 protein was uploaded in PyRx. The purified protein was then modified into a macromolecule by Pyrx,

which is done by adding Kollman charges and assigning every atom as Autodock4. Hence, the protein was converted into. pdbqt format from the .SDF format prior to docking. The 11 ligands that met the desired criteria were imported into PyRx. The energies of the ligands were then minimized and they were converted into the .pdbqt format through the Open Babel feature of PyRx [30]. For docking, the grid dimensions of Center X = 14.888, Center Y= 16.647 and Center Z= 51.5314 were chosen. The Top five compounds with the best binding scores, Vulgarin, Thujyl alcohol, iso-3-Thujyl acetate, (+)- alpha-thujone, and Verbenone were selected for further analysis.

Visualization

The structure of the ligand with the best binding affinity value was downloaded in the .PDB format. DS BIOVIA Discovery Studio Visualizer was used to obtain the 2D and 3D structure of the best performing ligand and the different protein-ligand interactions were also determined [26].

RESULTS

Protein Structure Analysis

Ramachandran Plot

Ramachandran Plot is a graphical representation of the dihedral angles (ϕ and ψ) of amino acid residues in protein structures. Ramachandran Plot is used to evaluate the accuracy and the stability of the protein structure. The Ramachandran plot for the purified protein PTPN22 was produced using PROCHECK. The secondary structure of PTPN22 protein was analyzed through PROSITE. The Ramachandran plot of purified PTPN22 revealed that out of a total of 297 amino acid residues, 82% (223 residues) were in the most favored region, 17.3% (47 residues) in the additionally allowed region and 0.7% (2 residues) in the generously allowed region. No residues (0%) were found in the disallowed region. Among the 297 residues, 272 were identified as non-glycine and non-proline, with 10 being glycine residues, 13 proline residues and 2 end residues (Figure 1).

According to the data generated by PDBsum, the predicted secondary structure of the protein PTPN22 consists of 2 sheets, 5 beta hairpins, 2 beta bulges, 10 strands, 11 helices, 14 helix-helix interactions, 25 beta-turns, and 1 gamma turn, as shown in Figure 2.

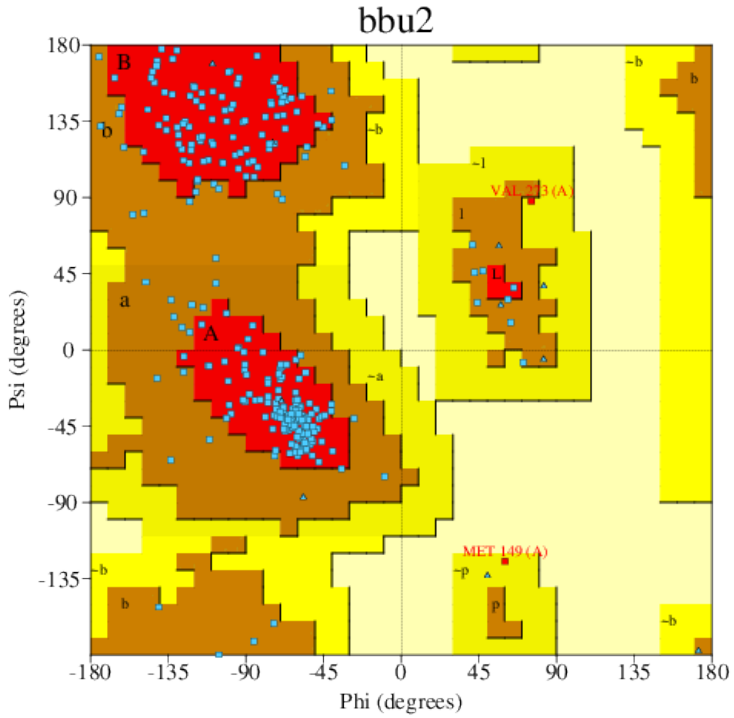

Figure 1. Ramchandran plot of PTPN22 protein using PDBsum.

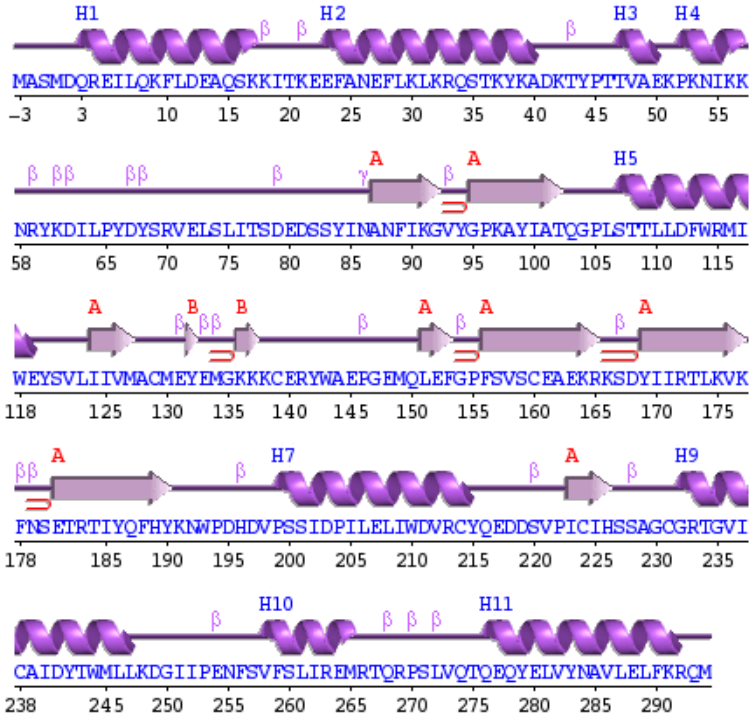

Figure 2. Secondary structure of PTPN22 protein using PDBsum.

Pharmacological Evaluation for Drug-Like Properties

A compound can be considered suitable for pharmaceutical use if it meets certain criteria including favorable physiochemical properties, a strong ADMET profile and adherence to Lipinski's rule of five. To ensure the production of medicines with fewer side effects, it is essential to analyze its toxicity data. As a part of this process, the ligands derived from *A. vestita* were subjected to pharmacological evaluation to identify their potential drug-like properties.

Physiochemical Analysis

The physiochemical assessment of the ligands was carried out using SwissADME, based on the following criteria (Table 1): Bioavailability score: ≥ 0.55, GI absorption: High, PAINS: 0 alert, Brenk: 0 alert, and Solubility: Very soluble or soluble. The top five ligands satisfy the above parameters, with no deviations observed in their properties as depicted in Table 2.

Table 1. Criteria for physiochemical characteristics.

Properties	Optimal Range
Solubility	Very soluble, soluble.
GI absorption	High.
Bioavailability score	O.55 and above.
PAINS	0 alerts.
Brenk	0 alert.

Table 2. Data for physiochemical characteristics of top five ligands.

Ligand	Bioavailability Score	GI Absorption	PAINS	Brenk	Solubility
Vulgarin	0.55	High	0 alerts	0 alerts	Soluble
Thujyl alcohol	0.55	High	0 alerts	0 alerts	Soluble
iso-3-Thujyl acetate	0.55	High	0 alerts	0 alerts	Soluble
(+)-alpha-Thujone	0.55	High	0 alerts	0 alerts	Soluble
Verbenone	0.55	High	0 alerts	0 alerts	Soluble

Lipinski's Rule Assessment

Lipinski's rule of five is a set of guidelines that evaluates the drug-likeliness and determines whether a compound meets the physical and chemical criteria required for it to be suitable for administration to humans. This rule evaluates drug-likeliness based on these guidelines: Molecular weight must be 150-500 Daltons, hydrogen bond donors must be <5, hydrogen bond acceptors must be <10, lipophilicity must be <5, octanol-water partition coefficient (LogP) must be <5 and the molar refractivity must be between 40 and 130 Å (Table 3).

The five leading ligands were evaluated using Lipinski's criteria and they met the specified parameters, with no violations (Table 4).

Table 3. Lipinski rule criteria.

Properties	Optimal Range
MW	150–500 Daltons
MlogP	<5
H donors	<5
H acceptors	<10
MR	40–130 Å

Table 4. Lipinski rule parameters of top five ligands.

Ligand	MW	M log P	H Donors	H Acceptors	Molar Refractivity
Vulgarin	264.32	1.62	1	4	69.83
Thujyl alcohol	154.25	2.45	1	1	46.86
iso-3-Thujyl acetate	196.29	2.76	0	2	56.59
(+)-alpha-Thujone	152.23	2.3	0	1	45.9
Verbenone	150.22	2.2	0	1	45.42

ADME Analysis

ADME analysis focuses on four key factors: Blood-Brain Barrier (BBB), Glycoprotein transportability (P-gp substrate), GI absorption and Solubility. The compound's ability to cross the Bood-Brain barrier (BBB) is essential to ensure the effectiveness of the drug and facilitate smooth drug formulation. High GI absorption and glycoprotein transportability (PGP substrate) are other key characteristics to consider for better drug efficacy. Additionally, the compound should also exhibit good solubility. Based on the data presented in Table 5, it is evident that the five compounds satisfied the required criteria, except P-gp-substrate which was negative for all the five compounds.

Table 5. Pharmacokinetic data.

Ligand	BBB	GI Absorption	P-gp Substrate	Solubility (LOGSw-SILICOS IT)
Vulgarin	Yes	High	No	–1.9
Thujyl alcohol	Yes	High	No	–1.46
iso-3-Thujyl acetate	Yes	High	No	–2.13
(+)-alpha-Thujone	Yes	High	No	–2.15
Verbenone	Yes	High	No	–2.13

Toxicity Prediction

Toxicity prediction involves assessing various important characteristics to evaluate the safety profile of the compounds. Factors, such as AMES toxicity, hERG blockers, H-HT, carcinogenicity, Rat Oral Acute (ROA) Toxicity, respiratory toxicity, skin sensitivity, and DILI are commonly analyzed. The toxicity profiles of the ligands based on the mentioned criteria were retrieved from ADMETlab and ProTox tool, the results of which are summarized in Table 6.

Table 6. Toxicity profile of ligands obtained from ADMET lab and ProTox server.

Ligand	hERG	H-HT	DILI	Ames	ROA	Carcinogenicity	Respiratory	Skin Sensitivity
Vulgarin	0.046	0.454	0.168	0.027	0.912	0.799	0.832	0.655
Thujyl alcohol	0.016	0.141	0.11	0.025	0.09	0.113	0.077	0.12
iso-3-Thujyl acetate	0.008	0.228	0.746	0.032	0.031	0.228	0.026	0.092
(+)-alpha-Thujone	0.026	0.262	0.479	0.161	0.713	0.821	0.888	0.348
Verbenone	0.004	0.128	0.377	0.015	0.389	0.622	0.961	0.591

Molecular Docking

The binding affinities of the selected ligands toward the PTPN22 protein were determined using Pyrx. For subsequent analysis, the model with the most significant binding energy was selected. The compounds which exhibited the most significant binding with PTPN22 were Vulgarin, Thujyl alcohol, iso-3-Thujyl acetate, (+)-alpha-Thujone, and Verbenone. These compounds showed a binding affinity of more than –5.5, as presented in Table 7.

Table 7. Binding affinities of the ligands toward PTPN22 protein.

Ligand	Binding Affinity with PTPN22
Vulgarin	–10.3
Thujyl alcohol	–7.3
iso-3-Thujyl acetate	–6.6
(+)-alpha-Thujone	–6
Verbenone	–5.6

Visualization

After docking, it was observed that the ligand Vulgarin with a binding affinity of -10.3, had the least binding with the receptor protein PTPN22. The receptor-ligand interaction of Vulgarin and PTPN22 protein was visualized in DS BIOVIA Discovery Studio Visualizer. The 2D and 3D structure of the interaction was retrieved, which is displayed in Figures 3 and 4. The 2D and 3D visualizations of the interactions clearly indicate that the ligand interacts with amino groups like Tyrosine (TYR), Serine (SER) and Lysine (LYS).

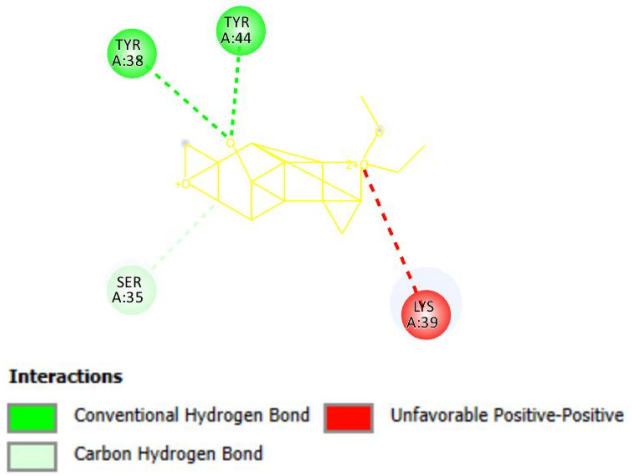

Figure 3. 2D visualization of interactions between PTPN22 protein and Vulgarin.

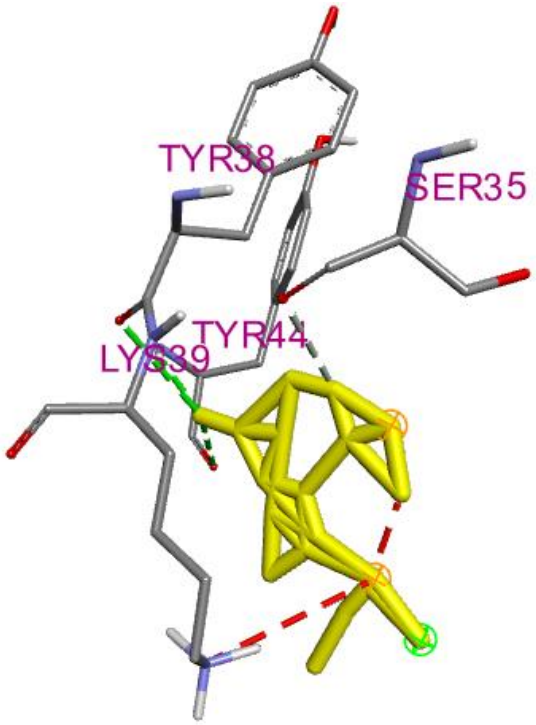

Figure 4. 3D visualization of interactions between PTPN22 protein and Vulgarin.

DISCUSSION

RA is an autoimmune condition that leads to joint damage and an increased risk of severe illness, causing 1 in 3 patients to become disabled [31]. It can also cause complications in extra-articular organs like the lungs, heart and other systems of the body [32]. The most common symptoms of arthritis include joint pain, swelling, stiffness and fatigue [33]. When extra-articular organs are affected, symptoms like low- grade fever and sweating are also observed [32]. TNF-α and IL-6 are the key cytokines involved in its pathogenesis [5]. The current treatment focuses on the use of DMARDs, NSAIDs and pain management [34, 35]. However, current therapies have drawbacks, such as potential side effects, chances of sensitivity with prolonged administration and high costs [34]. This indicates the need for safer and more accessible alternative or complementary treatments for RA.

The PTPN22 gene is believed to be a common risk factor in various autoimmune conditions, like RA [36]. Single nucleotide polymorphisms (SNPs) in PTPN22 which are linked to inflammation and autoimmunity are often associated with RA [37]. PTPN22 plays a fundamental role in causing immune dysfunction as it encodes a protein called tyrosine phosphatase which is expressed in many cells belonging to the innate and adaptive immune system [36].

Various studies have been conducted to assess the benefits of medicinal plants in treating RA to combat the limitations of conventional therapies. *A. vestita,* a medicinal plant that constitutes a major part of the grassland ecosystem is widely used in China and Tibet to treat inflammatory conditions, like RA [16, 38]. Studies have shown that extracts from *A. vestita* demonstrate anti-inflammatory properties, including suppression of mast cell degranulation as well as reduction in the production of inflammatory cytokines [16]. Flavones, like apigenin, cirsilineol and 6-methoxytricin from *A. vestita* have been found to be beneficial in reducing excessive immune response and inflammation [16].

This study focused on investigating the therapeutic potential of the phytochemical compounds derived from *A. vestita* for the treatment of RA using MD, a widely used technique in CADD. The compounds were docked with the receptor protein PTPN22 to assess their binding affinity with the

protein. The results of the docking revealed that the compounds with the best binding affinity toward PTPN22 were: Vulgarin, with a binding affinity of –10.3, Thujyl alcohol, with a binding affinity of –7.3, iso-3-Thujyl acetate, with a binding affinity of –6.6, (+)-alpha -Thujone, with a binding affinity of –6 and Verbenone, with a binding affinity of –5.6. Vulgarin exhibited the best binding toward PTPN22 as it had a binding affinity of –10.3. Vulgarin is an eudesmanolides-type sesquiterpene lactone [39, 40], with a Molecular Weight (MW) of 264.32. It is synthesized when 1-oxo-5αH, 6β, 11βH-eudesm-3-en-6, 13-olide is epoxidized and the resulting product is treated with silica gel [41]. It has been reported that Vulgarin has potential anti- inflammatory properties [39, 40]. Vulgarin also consists of α and β unsaturated ketones which contribute to its cytotoxic properties. The 2D and 3D structures of Vulgarin's interactions with PTPN22 were obtained from DS BIOVIA Discovery Studio Visualizer. The structures depicted that Vulgarin interacts with amino acids, like TYR, SER and LYS. Vulgarin's significant binding affinity toward PTPN22 and its therapeutic properties indicate that it is potentially a promising candidate for the treatment of RA. Followed by Vulgarin is Thujyl alcohol, which belongs to the class of compounds known as bicyclic monoterpenoids and has a MW of 154.25 g/mol. iso-3-Thujyl acetate is a type of monoterpene, with a MW of 196.2 g/mol. (+)-alpha-thujone, with a MW of 152.23 g/mol is the (1R, 4S, 5S)-stereoisomer of alpha thujone and an enantiomer of (–)-alpha-thujone. Verbenone with a MW of 150.22 g/mol is a carboxylic compound, a cyclic ketone and an enone. These compounds were subjected to physiochemical evaluation based on the criteria of Bioavailability score, GI absorption, PAINS and Brenk alerts and Solubility. The results of the physiochemical evaluation revealed that all the five compounds met the desired criteria with no violations. The compounds were also assessed according to Lipinski's rule of five and the results indicate that the compounds satisfied the required parameters, with no violations. ADMET filters were used to screen these compounds, and the results show that the compounds fulfilled the required parameters, except in the case of P-gp substrate which was negative for all the five compounds. The results of this study indicate that the ligands with the best affinity toward PTPN22 also have favorable drug-like properties which means that they can be considered viable candidates for the treatment of RA. Among the five compounds, Vulgarin was the most effective at targeting PTPN22, indicating that it is the most suitable compound for drug development for RA treatment.

This study aids in drug development as it employs computational methods to assess phytocompounds of *A. vestita* to identify the ones with drug-like properties. Using MD, the binding affinity of the compounds to PTPN22, a receptor protein involved in RA was determined, which helped in detecting the compounds which are most likely to have a promising impact in the treatment of RA.

CONCLUSIONS

This study aimed at evaluating the potential of phytocompounds derived from *A. vestita* as therapeutic agents for the treatment of RA using computational tools. RA is an autoimmune inflammatory disorder, primarily characterized by synovitis (inflammation of the synovial membrane) and is often accompanied by involvement of extra-articular organs. PTPN22 has been linked to arthritis as a significant susceptibility gene. PTPN22 has two key missense SNPs: R620W (C1858T, rs2476601) variant in exon 14 and R2630(G788A:rs33996649) variant in exon 10, which may contribute to autoimmunity observed in RA patients. This study makes a significant contribution in determining compounds from *A. vestita* with the most significant impact on PTPN22 using MD stimulations, which helps in identifying compounds which are most likely to be suitable candidates for developing treatments for RA. The study revealed that the compound Vulgarin showed the best binding affinity toward PTPN22, indicating that it is potentially the most promising compound for drug discovery. The study also assesses the pharmacological properties of the five phytocompounds, which helps determine whether the compounds possess drug-like properties. This facilitates the development of more effective plant-based therapies for RA treatment. Despite the valuable insights provided by this study, thorough clinical and laboratory testing is necessary to evaluate the real-life effectiveness and safety of the compounds, as this study only focuses on in silico analysis.

List of Abbreviations

A		
Absorption, Distribution, Metabolism, Excretion and toxicity	(ADMET)	9
Artemisia vesitia	(A. vestita)	8
B		
Blood-Brain Barrier	(BBB)	14
C		
Computer-Aided Drug Design	(CADD)	9
D		
Dassault Systems	(DS)	9
Disease-Modifying Anti-Rheumatic Drugs	(DMARDs)	7
G		
Gastrointestinal	(GI)	9, 10
I		
Indian Medicinal Plants, Phytochemistry and Therapeutics	(IIMPAT)	9
interleukin-6	(IL)-6	7
L		
Lysine	(LYS)	15
M		
Molecular docking	(MD)	9
N		
Non-Steroidal Anti-Inflammatory Drugs	(NSAIDs)	7
P		
Protein Data Bank	(PDB)	9
Protein tyrosine phosphatase non-receptor type 22)	(PTPN22)	7
Python Prescription	(PyRx)	10
R		
Rat Oral Acute	(ROA)	14
Rheumatoid arthritis	(RA)	7
S		
Serine	(SER)	15
Single nucleotide polymorphisms	(SNPs)	16
T		
Tumor necrosis factor -α	(TNF)-α	7
Tyrosine	(TYR)	15

Acknowledgment

We thank BioNome for their Guidance and support in our training and research project.

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