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Computational Drug Design and Molecular Docking Studies for the Identification of Potential Treatments for Vitiligo

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Abstract: Molecular docking is a widely used computational technique that models how ligands interact with protein targets, offering quantitative and qualitative information on binding affinity. It is a major component of Computer-Aided Drug Design (CADD), which plays a crucial role in modern drug discovery. CADD can be classified into Structure-Based Drug Design (SBDD), where docking is a primary tool, and Ligand-Based Drug Design (LBDD), which leverages information from known active compounds. Molecular docking makes it easier to identify and optimize medicinal medicines logically by accurately modeling ligand-protein interactions. Vitiligo is a chronic depigmenting disorder characterized by melanocyte loss due to oxidative stress and immune-mediated damage. In this study, selected ligands, including repurposed drugs and melanogenesis modulators, were evaluated against JAK1 and JAK2 using AutoDock 4. The docking results demonstrated strong and stable interactions, suggesting that compounds such as Ruxolitinib and Tofacitinib (JAK1 inhibitors) and other JAK2-targeted agents may serve as promising candidates for vitiligo therapy.

Keywords: *Drug Design, CADD, Molecular Docking, Autodock, Binding Energy, JAK1, JAK2, Fedratinib, Ruxolitinib, Tofacitinib, Baricitinib.*

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I. INTRODUCTION

In the past, drug discovery where biology and chemistry meet has been a laborious and expensive process that relies on traditional trial-and-error, frequently taking decades with unpredictable results. The introduction of Computer-Aided Drug Design (CADD) in the late 20th century completely changed discipline. CADD predicts the molecular interactions between a therapeutic substance and its target, which is usually a protein or DNA sequence, by combining computational algorithms with intricate biological data. The process of rational drug development is essentially accelerated by this predictive modeling, which is crucial for predicting a drug binding mechanism, pharmacological effects, and possible adverse responses. [1]

Melanocytes, the skin's pigment-producing cells, are lost in white patches of skin in vitiligo, an autoimmune skin condition. Vitiligo is a prevalent skin condition that affects 0.1 to 2% of people worldwide and is gender non-biased. Patients with vitiligo are more likely to get sunburns and develop skin cancer, and it has a major negative influence on their quality of life and sense of self. Vitiligo is a complex condition that involves autoimmune reactions, environmental factors that produce inflammatory mediators, and hereditary predisposition. Autoreactive CD8+ T lymphocytes, drawn to proinflammatory cytokines, are thought to encourage melanocyte death in vitiligo by destroying the pigment-producing cells of melanocytes via interferon-gamma (IFN-γ) signaling. Skin-resident memory T (TRM) cells are a subpopulation of T cells that live at the location of prior lesions' white spots rather than circulating, according to recent research. Thus, the most challenging aspect of treatment vitiligo relapse is caused by TRM cells.

One of the hardest dermatological problems to cure is vitiligo. Topical calcineurin inhibitors or steroids are the mainstays of actual therapies, which work best when paired with phototherapy. But over 40% of vitiligo patients experience a relapse within a year after ceasing treatment. The ideal treatment for vitiligo aims to prevent relapses, stop depigmentation, stimulate repigmentation, and stop the immune system from destroying melanocytes. MSCs contain immunomodulatory qualities that balance T-cell subsets and could stimulate melanocyte regeneration. Targeted treatments are currently undergoing testing because of significant advancements in the understanding of vitiligo pathophysiology and the use of MSC and other cellular therapies during the past several years. [2]

Molecular modeling is one of the powerful tools used by the research-based pharmaceutical business to analyze

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structure-activity relationships (SAR) in current medicinal chemistry. These approaches have also been used to study pharmacokinetic aspects (ADMET: absorption, distribution, metabolism, excretion, and toxicity) in addition to pharmacodynamic data (e.g., potency, affinity, effectiveness, and selectivity). [3] The process of docking involves analyzing how well the intended compounds fit into the target cavities and how they interact with the residues. Docking, such as protein-ligand docking, is typically done between tiny and macromolecules in the computational drug development process. Molecular docking is the term for this kind of docking. In recent years, docking has also been carried out between two macromolecules, such as protein-protein docking. [4]

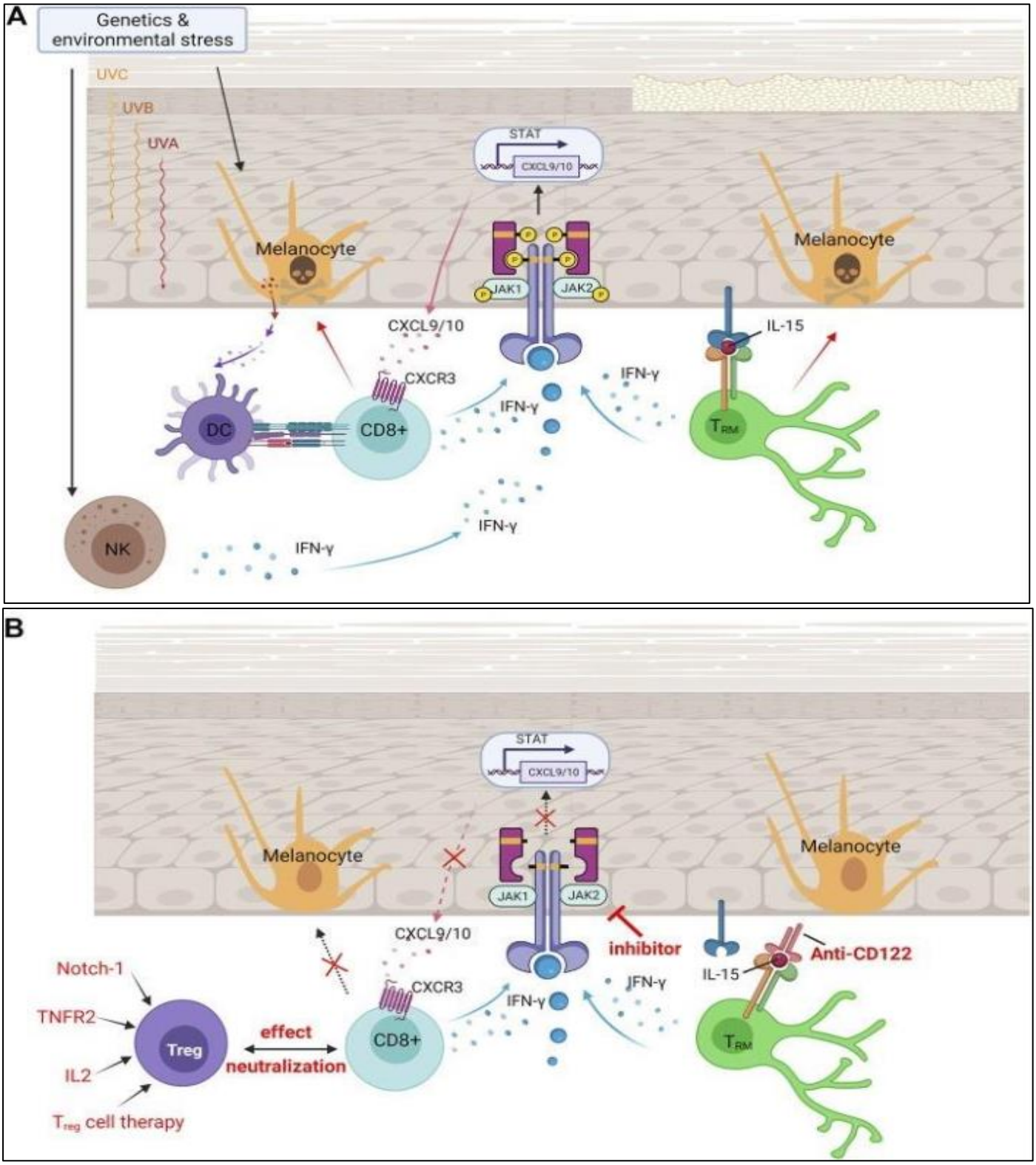

Fig 1 Vitiligo Pathogenesis and Currently Available Treatments for Vitiligo. (A) Pathologies of Vitiligo. (B) Immunomodulated Therapeutic Intervention in Vitiligo.[2]

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II. DRUG DISCOVERY & DEVELOPMENT

Drug discovery is a very expensive and time-consuming process that is required to ensure the quality and safety of new therapeutic entities that are introduced to the market. According to reports, the various stages from target assessment to regulatory approval can take up to 14 years and cost more than $1 billion for a single innovative small chemical. Furthermore, it is well known that the pharmaceutical industry has one of the highest failure rates. In fact, just one or two of every 10,000 examined compounds are thought to have the potential to become medications.

The vastly expanded chemical space that forms the "drug-like" environment is another significant obstacle in the medical realm. According to calculations, there would be approximately 1060 tiny molecules in such a concept, which is more than the number of seconds of existence in the entire universe. From an experimental standpoint, it is even more impossible to study such a large chemical area. In fact, the capacity of the most advanced high-throughput screening (HTS) techniques available today would never match the order of magnitude of the possible candidates for that biological entity, even if they were able to assess the on-target activity of hundreds of thousands of compounds per week.

Medicinal chemists can get over this restriction by moving the candidate selection problem from a lab setup to a "virtual environment." Using computers to conduct molecular "virtual" screenings prior to the experimental ones was one of the initial concepts that emerged. This method, formerly known as "high-throughput virtual screening" (HTVS), continues to be one of the primary uses of computational techniques in drug development. [5]

- *The Application of Computational Methods in Drug Discovery*

The United States Food and Drug Administration (US FDA) states that there are five primary steps in the drug discovery process. The first stage is called "discovery and development," and it involves lead optimization, hit-to-lead (H2L), and hit identification. The first of these involves discussing pharmacokinetic (PK) or pharmacodynamic (PD) limits in addition to identifying a few molecular candidates with a promising activity profile against the intended target. In terms of on-target potency, the hit compounds are typically not very selective and have action in the micromolar (μM) range. Despite all these pharmacological issues, the hit compounds are crucial for providing the drug design teams with some guidance and are excellent places to start when making additional changes.

The hit-to-lead optimization step is covered in the second passage. To enhance their on-target activity and selectivity, the hit compounds are altered using several techniques in this step, all the while closely monitoring their PK/PD profile. Following this procedure, the refined molecular candidates are referred to as "lead" compounds, and they are often highly active (potency-wise, in the nanomolar range) and selective. After that, these substances move on to the second major stage, the preclinical experimental phase, where their safety and effectiveness are evaluated using animal and organoid models. Clinical trials involving humans make up the third and longest phase.

These are separated into three major sections (I, II, and III), each of which has an increasing number of patients engaged in the tests and a distinct endpoint. The commercialization of the medication can be requested by the regulatory bodies (such as the FDA in the USA and EMEA in Europe) shortly after the therapy with the new candidate in clinical phase III shows promise. This will determine the start of the fourth stage of drug development. Subsequently, post-market medication safety monitoring is the final and fifth phase. [5]

- *CADD*

All computer-assisted methods for discovering, design, and optimizing biologically active molecules having the potential to be utilized as medications are referred to as computer-aided drug design. Target selection, lead identification, and clinical candidate selection are the three pre-clinical steps of the drug development process that precede clinical trials. Rapid advancements in structural biology and computer technology have made structure-based computer-aided drug design (CADD), which uses docking techniques, virtual screening and library design, as well as target/structure focusing combinatorial chemistry, a potent tool in the multi-step phase of drug development.

To turn physiologically active molecules into suitable medications by improving their physicochemical, pharmaceutical, and ADMET/PK properties, CADD is used to identify active drug candidates, select leads, and optimize leads. In pharmaceutical research, the term "biological target" is often used to refer to the native protein in the body whose activity is altered by a medication, producing a desired therapeutic effect.

- *Capabilities of CADD Include:*

Virtual screening of datasets with over 6 million different chemicals employing high-throughput docking, 2D similarity searches, and 3D pharmacophore searches Target-focused compound library design; lead optimization using structure- or ligand-based design; chemical library profiling and filtering for molecules with desired drug-like and DMPK properties; quantitative structure activity relationships (QSARs) establishment; computer modeling of DMPK properties, including CYP inhibition and metabolism

- *The Following are the Two Primary Techniques to Drug Design Using CADD:*

- Direct approach/ Structure-based medication design
- Indirect approach/ Ligand-based drug design [6]

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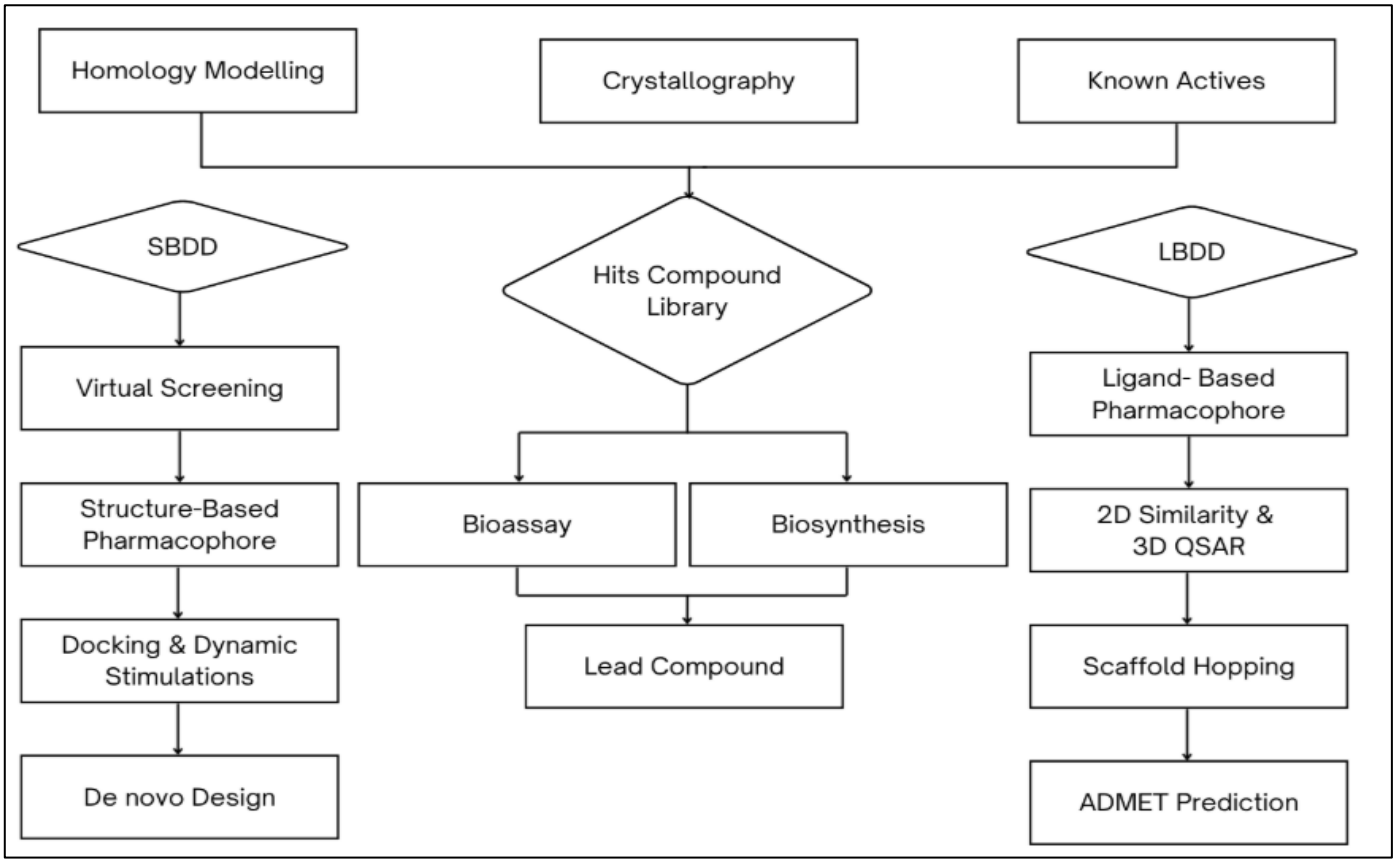

Fig 2 Conventional Pathways in Structure-Based Drug Design (SBDD) and Ligand-Based Drug Design (LBDD) Employ Distinct Methodologies. SBDD Centers on Target Biomolecule Structures, While LBDD Relies on Known Ligand Characteristics [1]

➢ *Structure-Based Drug Design (SBDD)*

The trend in computational drug design methodologies shifted toward alternative approaches that could also consider the three-dimensional interactive features of the molecules with respect to the target due to the exponential growth in the availability of three-dimensional structures of proteins and nucleic acids, which began about in the 2000s. In fact, the scientists were greatly aided by their prior understanding of the biological entity of interest, which allowed them to create new chemical species based on the properties of its binding site. The family of "structure-based drug design" (SBDD), which is by far the most popular method in computational drug discovery, includes all techniques based on this type of data.

SBDD is lock-and-key binding, in which a drug molecule attaches itself to a particular location on the target protein in a manner like how a key fits into a lock. Depending on the type of interaction, the drug molecule binding to the target protein may either promote or inhibit the protein function. Finding the target protein's three-dimensional structure is the initial stage in SBDD. Techniques like cryo-electron microscopy, NMR spectroscopy, and X-ray crystallography can be used to do this. Finding tiny compounds that can attach to the target protein and alter its activity comes next once the target protein structure has been determined.

A computational method for predicting how tiny compounds will connect to the target protein is called "molecular docking." Molecular docking involves screening a library of small molecules for their capacity to attach to the binding site of the target protein. For additional testing, the compounds that exhibit the best fit are chosen. [7]

➢ *Ligand-Based Drug Design (LBDD)*

Ligand-based drug design (LBDD), another name for indirect drug design, helps find new small compounds that bind to protein targets. To predict putative active sites, generate similar structures, perform molecular docking with active ligands, catalyze binding interactions, and optimize the lead ones to improve their binding properties, efficacy, and safety, the drug molecules supported by bioinformatics tools are identified by the silico procedures used here. These molecules are then further investigated on various platforms.

Substances can now be identified as targets very systematically using specific, state-of-the-art computational techniques because there is no reliable 3D macromolecular structure. The potency of a lead compound as well as its absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics are predicted using matched molecular pair (MMP) analysis, Free-Wilson models, and quantitative structure-activity relationship (QSAR) models based on experimental data sets.

Conformational analysis plays a major role in determining the flexibility and behavior of molecules for bioactive conformation.

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➢ *Quantitative Structure Activity Relationships (QSAR)*

Quantitative Structure-Activity Relationship (QSAR) is a useful technique for drug design, which is a crucial step in the process of finding novel medications. Using characteristics known as molecular descriptors, QSAR is a statistical method that connects a molecule's structure to its biological activity. Because of this, QSAR is a useful technique for creating medications that work. Density Functional Theory (DFT)-based chemical characteristics are used by QSAR to investigate compounds.

Since they describe the molecular characteristics associated with activities, selecting the appropriate descriptors from a wide range of alternatives is a major challenge. To enhance the study of these activities, new QSAR techniques have been created.[8]

- *Different Descriptors:*

✓ Topological descriptor
✓ Geometrical descriptor
✓ Molecular descriptor
✓ Thermodynamic descriptor
✓ Constitutional descriptor
✓ Electronic descriptor

III. MOLECULAR DOCKING

➢ *Aim:*

The primary goal of the docking technique is to determine the optimal conformation for both the ligand and the receptor by determining the optimal manner for a ligand to engage an active site. To attain orientation between a protein and a ligand while minimizing the amount of energy used. Its main significance is in determining the proper binding location. The prediction of binding affinity. How important it is to design a medicine

➢ *Objective:*

- Ligand-protein docking is an optimization issue that relies on ligand energy position prediction.
- Single-objective and multi-objective methods are typically used to solve molecular docking problems to decrease the binding with the lowest binding energy in the receptor's active site.
- A novel multi-objective formulation that considers the binding (intermolecular) energy and the Root Mean Square Deviation (RMSD) variation in ligand coordinates as two objectives to assess the quality of the ligand-protein interactions.
- Using multi-objective algorithms to identify a group of representatives.
- The performances have been evaluated using two primary quality indicators designed to gauge front variety and convergence.
- Additionally, AutoDock, a reference single-objective evolutionary method for molecular docking, is compared with LGA.
- In silico docking investigations to choose novel anticancer drugs for therapeutic targets that are multidrug resistant, this new multi-objective approach demonstrates an improvement over the ligand-protein docking predictions that may be promising. [10]

➢ *Scope*

Molecular docking and computer-aided drug design (CADD) offer a quick and economical way to find and refine possible therapeutic candidates prior to laboratory testing. By predicting how tiny molecules interact with biological targets, these techniques enable early screening of drugs with attractive pharmacokinetic profiles and high binding affinities.

Docking makes it possible to compare several pharmacological compounds for target specificity, identify important binding residues, and visualize ligand–protein interactions. Supporting lead optimization, ranking compounds for synthesis, cutting down on experimental burden, and expediting the entire drug development process are all included in the scope.

When combined, CADD and docking provide a potent platform for logical drug design, target validation, and the identification of promising therapeutic compounds for additional in-vitro, in-vivo, and clinical testing.

➢ *Principles of Molecular Docking*

Molecular recognition is a major problem in structural biology. Whether they are big macromolecules or small ligands, molecules must interact in almost every biological event. For almost a century, medicinal chemists have tried to precisely modify these interactions. We must be able to both comprehend and predict the structural features of recognition events to produce therapeutic medications more rapidly. If we had a complete understanding of the basis for complementarity, we could make predictions for the purpose of drug design.

Molecular docking has emerged as a critical component of computer simulation-based drug development in recent years. This approach involves predicting how a protein will interact with a tiny chemical at the atomic level. This enables researchers to understand proteins and the fundamental metabolic mechanism involved in this interaction by looking at the activities of small compounds, such as nutraceuticals, inside the target binding region. The approach works well. The technique depends on the target protein structure, which needs to be acquired utilizing technology in a high-resolution three-dimensional format. Analysis techniques include X-ray crystallography, NMR spectroscopy, and cryo-EM7.

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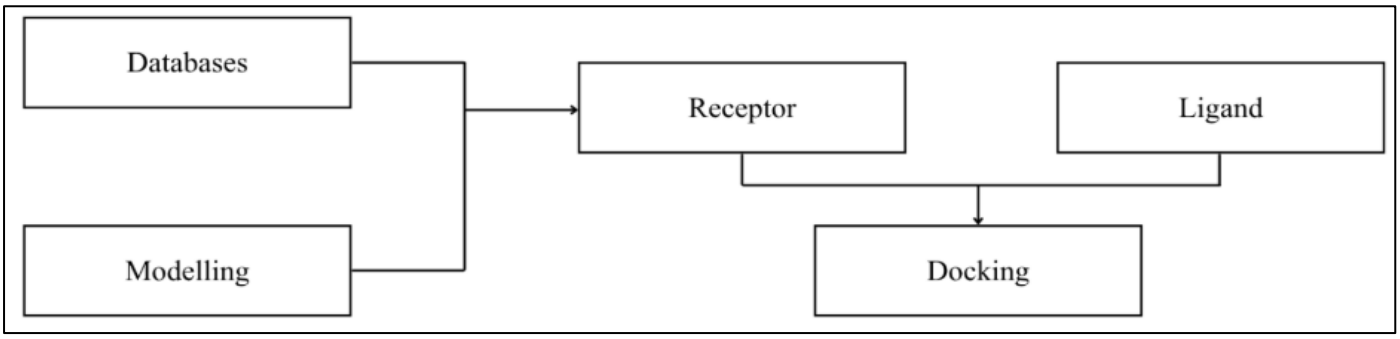

Fig 3 Basic Molecular Docking Procedure [9]

- *Docking Types Include:*

✓ Rigid docking (lock and key): Where a ligand and receptor have rigid geometries.
✓ Flexible docking: In this kind of docking, molecules rotate with each rotation.

The characteristics of assessed docking programs

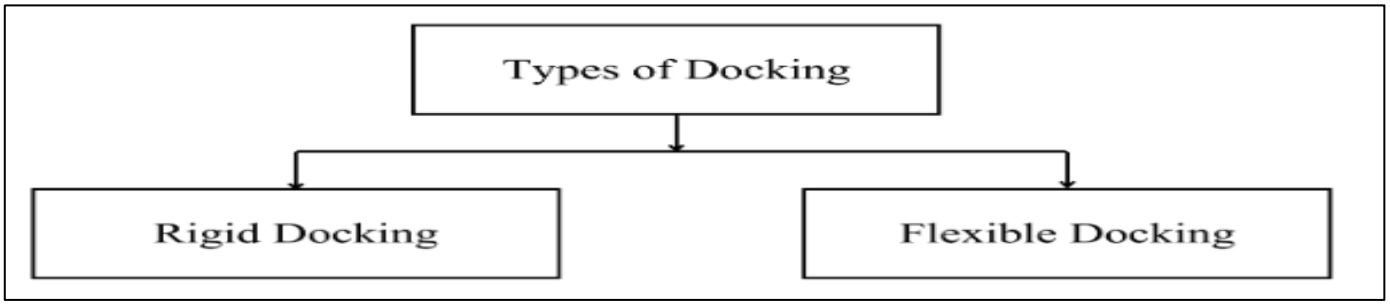

Fig 4 Types of Docking

- *Docking Can be Between*:

✓ Protein- ligand.
✓ Protein- protein.
✓ Protein- nucleotide.

- *Types of Interactions:*

✓ Electrostatic forces.
✓ Electrodynamics forces.
✓ Steric forces.
✓ Solvent related forces.

- *Key Stages in Docking*

✓ Target selection and preparation
✓ Ligand selection
✓ Docking-Evaluating docking result [10]

➢ *Various Docking Approaches:*

- *The Monte Carlo Method:*

This method works well for creating a ligand's initial orientation at the active site with translation and random conformation rotation. It has the ability to score both the initial orientation and a newly generated arrangement. The ability of a new configuration to be retained can be assessed using a metropolis criterion. The Metropolis criterion is predicated on accepting new solutions right away, but only if they are superior to the preceding one. If a configuration is determined not to be novel, a Boltzmann-based probability function is used.

- *Fragment-Based Approach:*

As the name implies, this approach primarily relies on the division of ligands into fragments or little protons, which is then followed by the docking process and, lastly, the joining of docked fragments.

- *Distance Geometry:*

Intramolecular or intermolecular distances have been used to communicate information about the structure. This geometry first calculates the distance and then the consistency of 3-d structures is calculated with these distances.

- *Matching Approach:*

The complementarity between the ligand and the protein serves as the fundamental foundation of the matching strategy. This method creates the ligand-receptor configuration by positioning the ligand atom at the optimal location within the protein. This configuration may need to be further optimized.

- *Ligand Fit Strategy*:

This strategy is based on the shape of similarity between the active regions of proteins and ligands. As a result, it helps with quick and precise techniques for docking ligands of

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smaller molecules into protein active sites.

- *Point Complementarity Approach:*
  This method seeks to assess the chemical complementarity and shape of the molecules that create interactions.

- *Blind Docking:*
  This docking technique is used to identify potential binding locations. Additionally, the targeted proteins' entire surface can be scanned to determine the peptide ligand's fashion.

- *Inverse Docking:*
  This docking process makes use of computer techniques to identify the side effects and toxicity of small molecular protein targets. The comprehension of these proteins' capabilities

➢ *Application of Molecular Docking:*

- *Hit Identification:*
  Docking offers quick in silico screening of a vast array of possible treatments to find molecules capable of binding to a single target of interest when combined with a scoring algorithm.

- *Lead Optimization:*
  A technique for predicting the precise location and distance of a ligand's connection to a protein is docking, often known as the binding mode or pose. Using the previously provided data, more accurate and powerful mimics can be produced.

- *Drug Discovery:*
  Molecular docking is used to find potential pharmacological substitutes by predicting how small molecules will attach to a polypeptide or receptor. A lead compound structure can also be altered to increase its binding affinity and selectivity.

- *ADMET Prediction:*
  Molecular docking may be able to mimic small molecule characteristics such Shock Absorption, Distribution of Benefit, Metabolism or Flushing, and Neurotoxicity (ADMET, which stands).

- *Structure Elucidation:*
  Molecular docking can help confirm the structures of antibodies with ambiguous geometries.

- *Target Fishing:*
  Molecular docking can be used to identify particular proteins that the drug may work through.

- *Nutraceutical Research:*
  Molecular docking can be used to better define the cellular targets of nutraceuticals for medical usage.

- *Bioremediation:*
  Molecular docking can be used to identify enzymes and how they are activated. Finding connections between proteins is also crucial. The restoration treatment is used to electronically examine molecules. [8]

IV. MATERIALS AND METHODS

The method entails studying the intermolecular interactions between two molecules, such as a ligand and receptor, in silico. The protein receptor is a macromolecule, and the ligand is a macromolecule that functions as an inhibitor. The method includes:

➢ *Step I: Identification of Molecular Target*
The crystal structures of the molecular targets were selected based on an extensive literature survey. JAK1 (PDB ID: 6BBU) and JAK2 (PDB ID: 7RN6) were retrieved from the RCSB Protein Data Bank for further analysis.

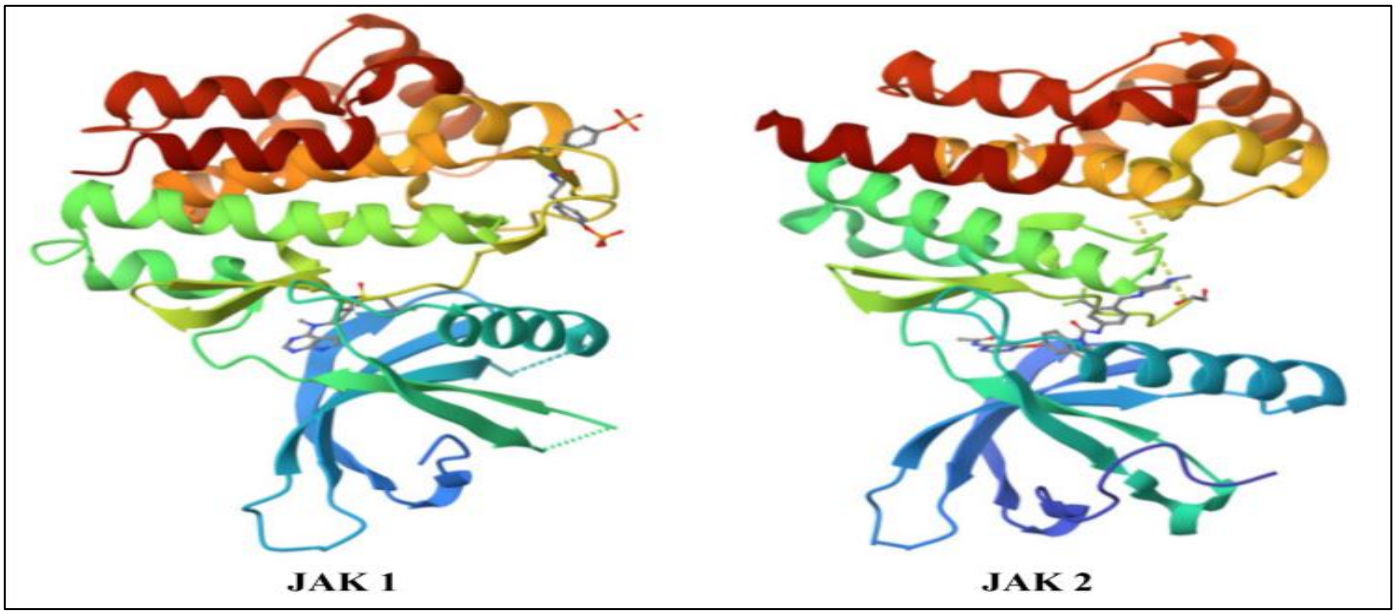

Fig 5 Structure of Protein (A) 6BBU and (B) 7RN6

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➢ *Step II: Target Protein Preparation*

The target protein crystal structure was loaded into UCSF ChimeraX for preprocessing after being obtained from the RCSB Protein Data Bank (PDB). All non-standard residues and heteroatoms were selected and deleted. The processed protein structure was then saved as protein.pdb for further docking studies.

➢ *Step III: Ligand Selection and Preparation*

The ligand was selected from the PubChem database and downloaded in 3D SDF format. It was then opened in Avogadro, where hydrogens were added, and geometry optimization was performed until the structure stabilized. The optimized ligand was saved in ligand. Mol 2 format for further use.

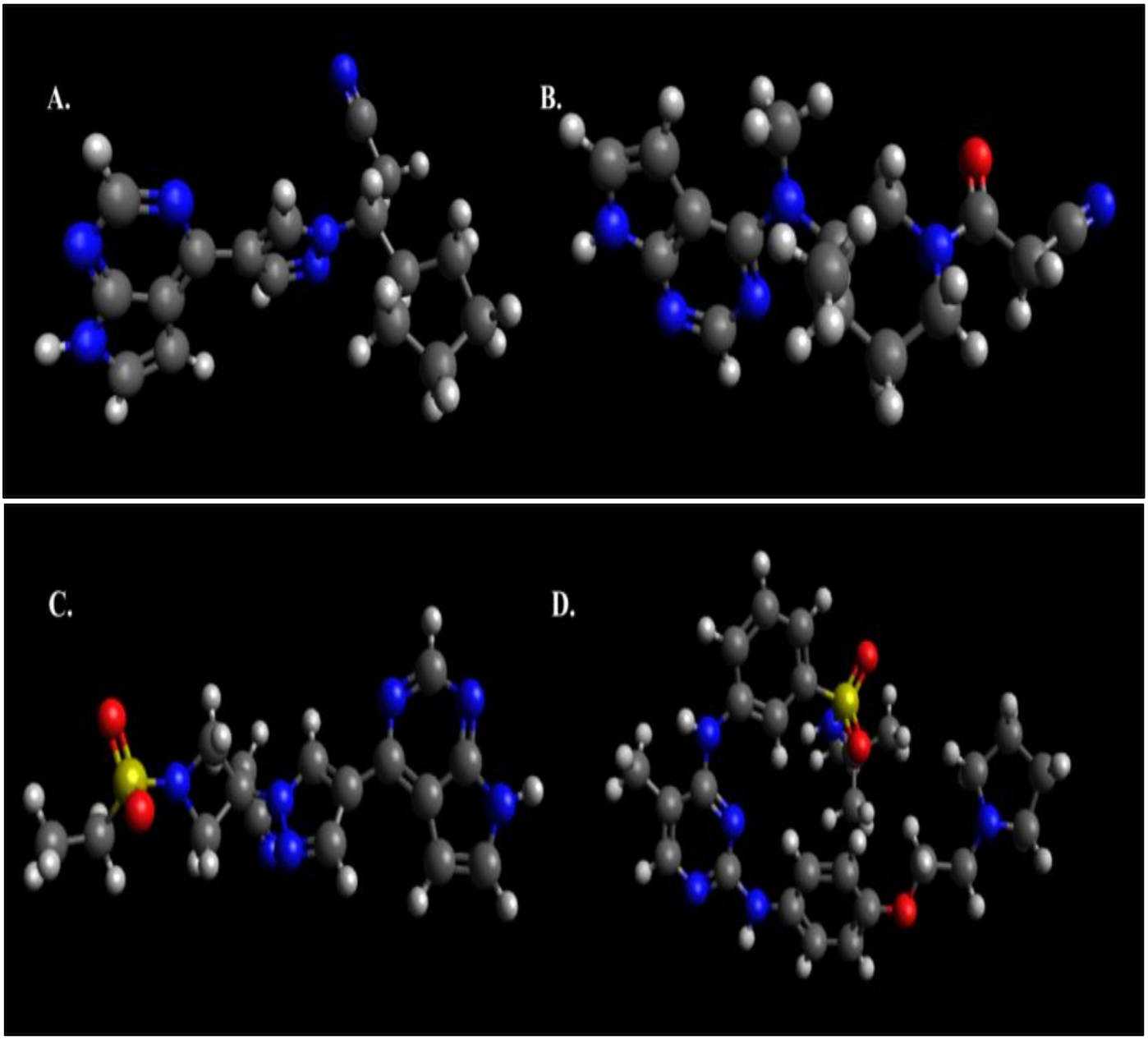

Fig 6 (A) Ruxolitinib, (B) Tofacitinib, (C) Baricitinib, (D) Fedratinib

➢ *Step IV: Docking*

The prepared ligand (ligand. Mol 2) and target protein (protein.pdb) were subjected to docking using Auto Dock. The resulting docked complexes were analyzed, and the best binding conformation was selected based on the lowest binding energy for further studies.

➢ *Step V: Prediction of Active Site*

Active site prediction and interaction analysis for the Janus kinase (JAK) proteins were performed using Auto Dock and visualized with Auto Dock Tools (ADT).

For JAK1 (PDB ID: 6BBU), the active site was defined by ARG1129, TRP1132, ARG1113, GLY1111, PHE1134, GLN1135, and GLU1133. The binding of the standard inhibitor Ruxolitinib was confirmed within this pocket, validating the prediction. In contrast, the inhibitor Tofacitinib interacted with a different residue set: GLU1012, LEU959, SER361, PRO960, PHE958, and GLN904.

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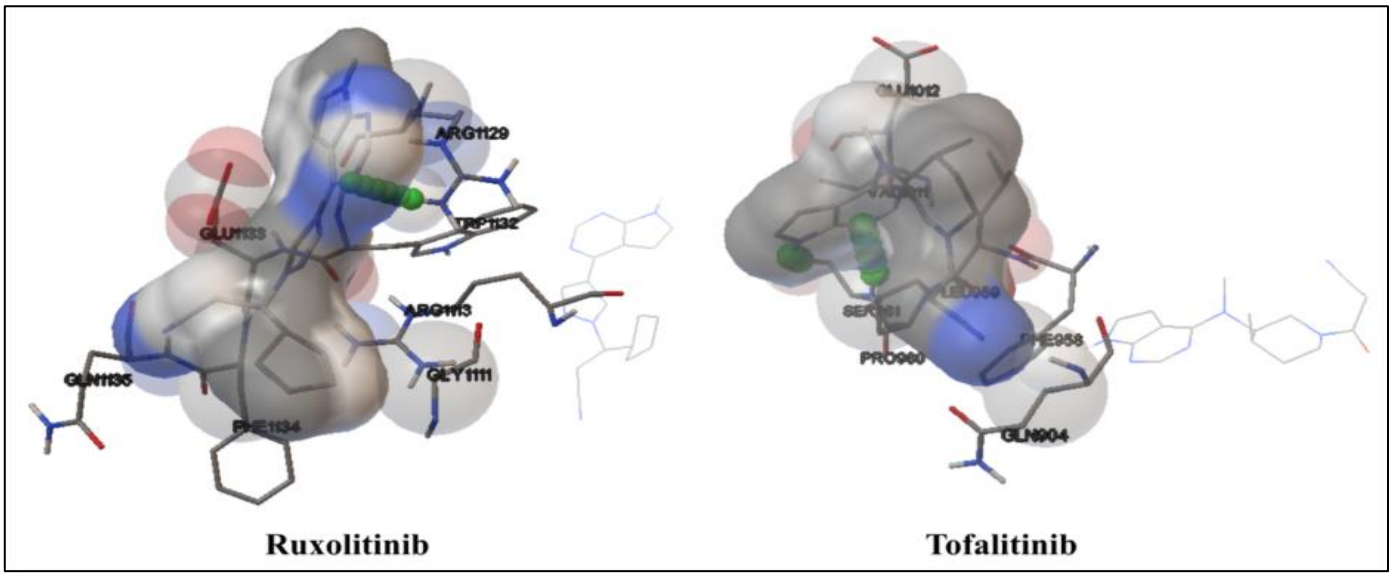

Fig 7 Binding Modes of Ligands with JAK 1 (6BBU)

For JAK2 (PDB ID: 7RN6), the active site residues included: ARG975, ARG897, GLU898, GLY993, ILE901, LEU905, LEU967, HIS974, TYR974, and ILE973. The docking of the standard inhibitor Baricitinib confirmed this site. The inhibitor Fedratinib exhibited binding primarily with SER1054, ILE1051, TYR1050, ILE943, GLU946, LYS945, and GLN942.

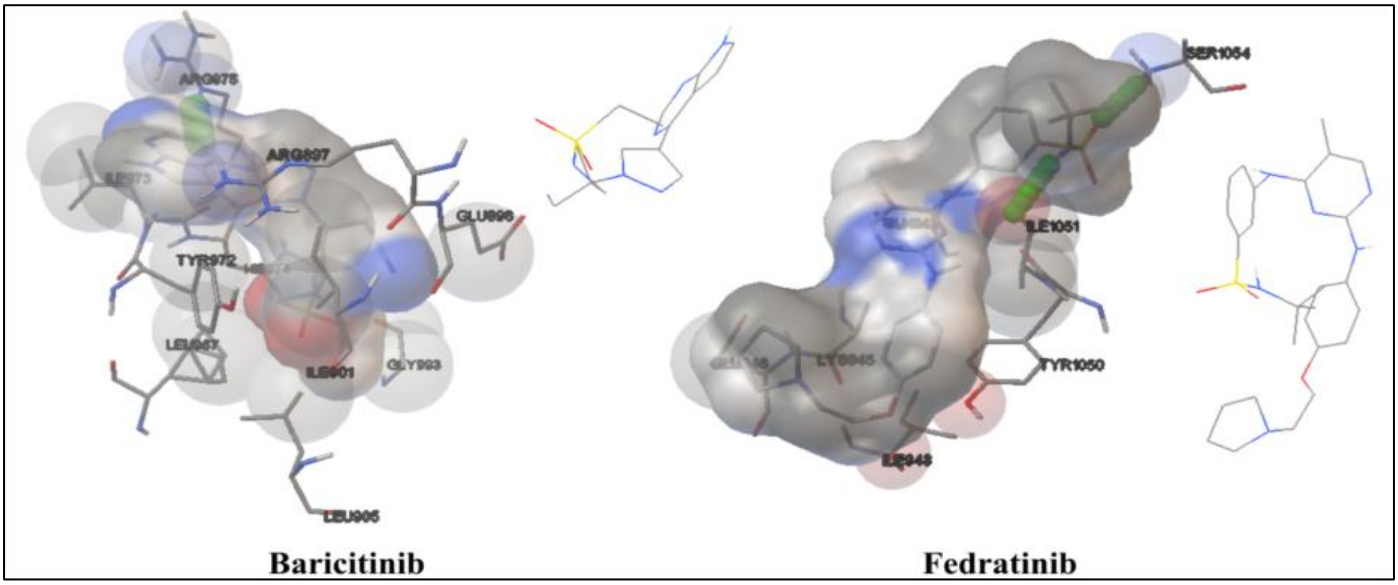

Fig 8 Binding Modes of Ligands with JAK 2 (7RN6)

Table 1 Tools

Technique/ Software	Key Features	Website
UCSF ChimeraX	Protein preparation, visualization, and analysis of molecular interactions.	https://www.cgl.ucsf.edu/chimera/
Avogadro	Ligand structure building, optimization, and energy minimization.	https://avogadro.cc/
MGL Tools (Auto Dock)	Molecular docking and binding affinity prediction.	https://ccsb.scripps.edu/mgltools/
BIOVIA Discovery Studio Visualizer	Visualization of docked complexes and interaction analysis.	https://discover.3ds.com/discovery-studio-visualizer-download
Swiss ADME	Prediction of pharmacokinetic and drug-likeness properties (ADME).	http://www.swissadme.ch/
Pro Tox-II	Toxicity prediction and LD_{50} estimation of compounds.	https://tox-new.charite.de/protox_II/

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V. ADMET PREDICTION

The canonical structures of Fedratinib, Ruxolitinib, Tofacitinib, and Baricitinib were retrieved from PubChem and analyzed for ADME properties using SWISSADME (http://www.swissadme.ch/index.php). Their pharmacokinetic profiles, including absorption, distribution, metabolism, excretion, and toxicity (ADMET), were examined. Ruxolitinib, Tofacitinib, and Baricitinib showed high GI absorption, while Fedratinib was low; all were non-BBB permeant. Ruxolitinib and Baricitinib were P-gp substrates, CYP inhibition was predicted for Ruxolitinib and Fedratinib.

All ligands satisfied drug-likeness rules, with acceptable lipophilicity, skin permeability, and bioavailability, supporting their suitability for docking studies. Furthermore, the toxicity prediction for oral consumption of Fedratinib, Ruxolitinib, Tofacitinib, and Baricitinib was calculated using Protox II (tox.charite.de). This prediction aids in evaluating carcinogenicity, hepatotoxicity, immunotoxicity, and other toxicological pathways.

Table 2 ADME Analysis

	Fedratinib	Ruxolitinib	Tofacitinib	Baricitinib
GI Absorption	Low	High	High	High
BBB Permeant	No	No	No	No
P-gp Substrate	No	Yes	No	Yes
CYP Inhibition	Yes	Yes	No	No
Log P	3.90	1.75	2.0	0.55
Log Kp (cm/s)	-6.12	-6.66	-7.14	-8.89
Bioavailability	0.55	0.55	0.55	0.55

Note: Log Kp = Skin Permeation

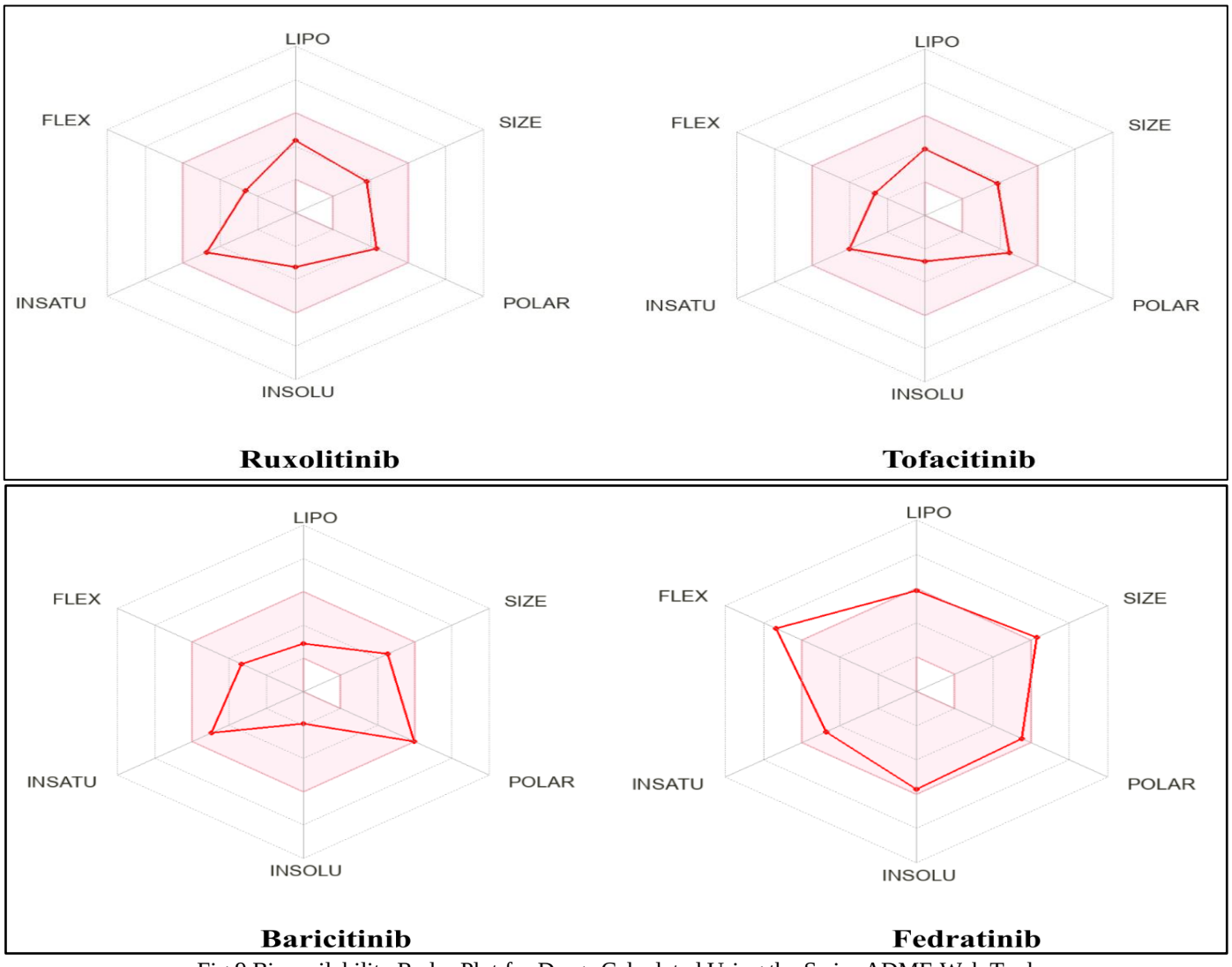

Fig 9 Bioavailability Radar Plot for Drugs Calculated Using the Swiss ADME Web Tool

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➢ *Toxicity Prediction*

Fig 10 Toxicity Radar Chart of Drugs Showing Organ and Endpoint Predictions Generated Using Pro Tox-II

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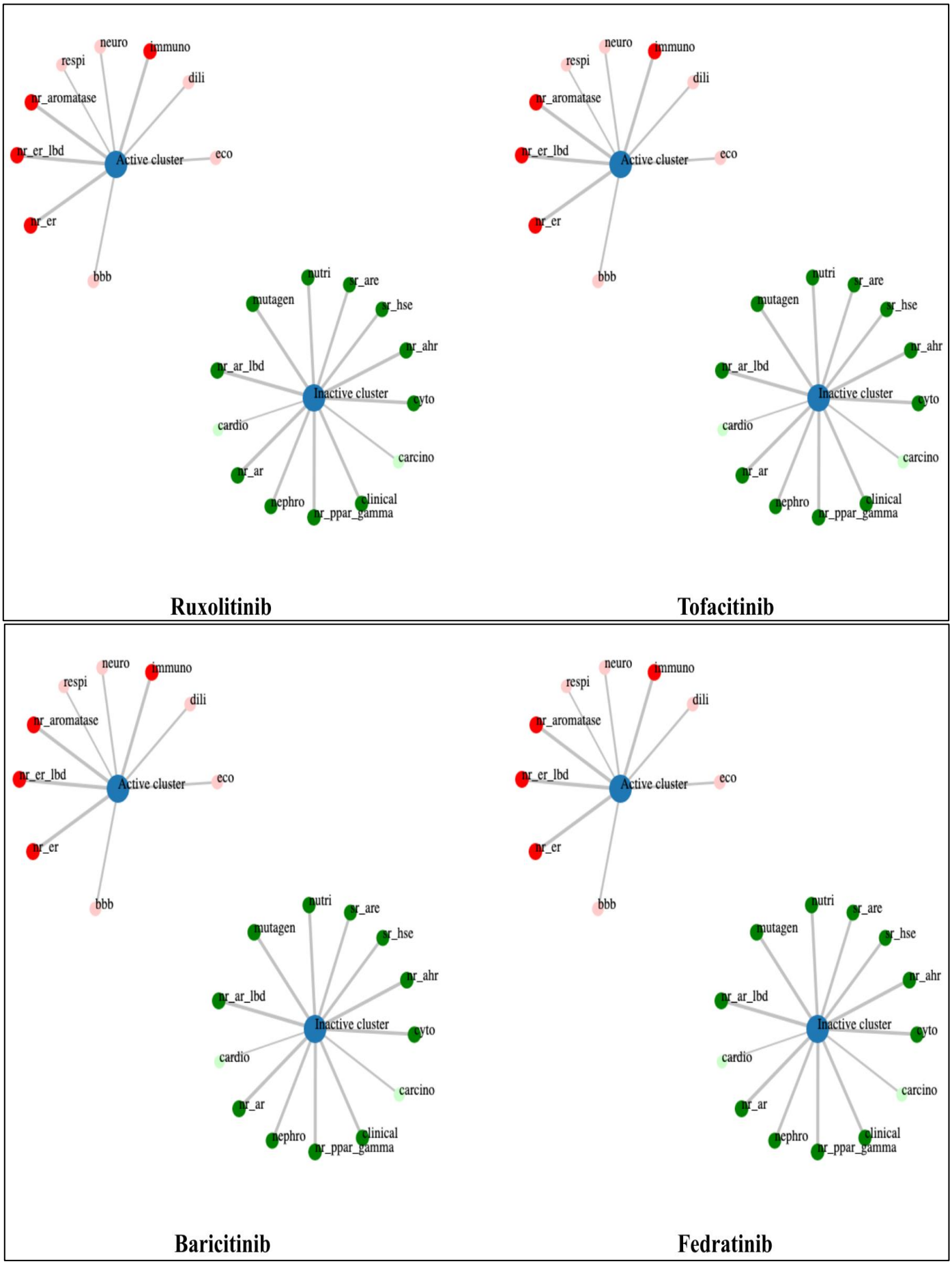

Fig 11 Network Chart of Drugs Predicted Toxicity Targets Generated Using Pro Tox-II

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VI. RESULTS

Auto Dock 4.2.6 was used to perform molecular docking investigations of four JAK inhibitors against the target proteins JAK1 and JAK2: Ruxolitinib, Tofacitinib, Baricitinib, and Fedratinib. Each chemical's docking results were examined using binding affinity (kcal/mol) and inhibition constant (Ki). Tables 3-6 summarize the information gathered from ten docking runs for each compound.

➢ *For JAK1:*

Docking studies of Ruxolitinib and Tofacitinib were carried out using Auto Dock 4.2.6 Each ligand underwent ten docking runs, and results were analyzed for binding energy. The detailed docking outcomes are presented in Tables 3 and 4

Table 3 Molecular Docking Results of Ruxolitinib with JAK1.

Cluster Rank	Run	Binding Energy (kcal/mol)
1	1	-8.50
1	4	-7.97
2	8	-8.06
2	6	-7.09
3	5	-7.93
3	7	-7.72
4	9	-6.29
5	2	-6.00
6	10	-5.84
7	3	-5.37

Table 4 Molecular Docking Results of Tofacitinib with JAK1.

Cluster Rank	Run	Binding Energy (kcal/mol)
1	1	-7.02
2	8	-6.43
3	5	-6.43
4	9	-6.21
4	2	-6.15
4	4	-5.76
5	7	-6.18
5	6	-5.81
6	10	-5.74
7	3	-5.10

➢ *For JAK2*

Docking studies of Baricitinib and Fedratinib were carried out using the same protocol. Ten runs were performed for each compound, and the corresponding docking results are summarized in Tables 5 and 6.

Table 5 Molecular Docking Results of Baricitinib with JAK2

Cluster Rank	Run	Binding Energy (kcal/mol)
1	6	-7.69
1	4	-7.63
1	9	-6.92
2	10	-7.14
3	5	-6.69
3	8	-6.67
3	7	-6.57
4	2	-6.45
5	1	-6.26
6	3	-5.23

Table 6 Molecular Docking Results of Fedratinib with JAK2

Cluster Rank	Run	Binding Energy (kcal/mol)
1	9	-9.44
2	3	-8.07
3	7	-7.08
4	1	-6.38

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5	8	-5.94
6	2	-5.74
7	5	-5.61
8	4	-4.64
9	6	-4.43
10	10	-3.97

➢ *Comparative Docking Analysis*

Among all four ligands, Fedratinib (JAK2) showed the lowest binding energy (−9.44 kcal/mol), indicating the strongest affinity toward the target protein. It was followed by Ruxolitinib (JAK1), Baricitinib (JAK2), and Tofacitinib (JAK1). These results suggest that Fedratinib exhibits superior docking performance and potentially higher inhibitory efficiency compared to the other compounds.

Table 7 Comparative Docking Results of the Four Compounds

Sr. No.	Target	Name of the Compund	Cluster Rank	Binding Energy (kcal/mol)
1	JAK1	Ruxolitinib	1	-8.50
2	JAK1	Tofacitinib	1	-7.02
3	JAK2	Baricitinib	1	-7.69
4	JAK2	Fedratinib	1	-9.44

VII. DISCUSSION

➢ *Molecular Docking Studies*

Ruxolitinib stably binds to the JAK1 active site (Figure 12) through hydrogen bonds with ARG1129, PHE1134, and GLN1135. Its binding energy (-8.50 kcal/mol) supports reported JAK1 and Ruxolitinib interactions, confirming its potential as an effective JAK1 inhibitor.

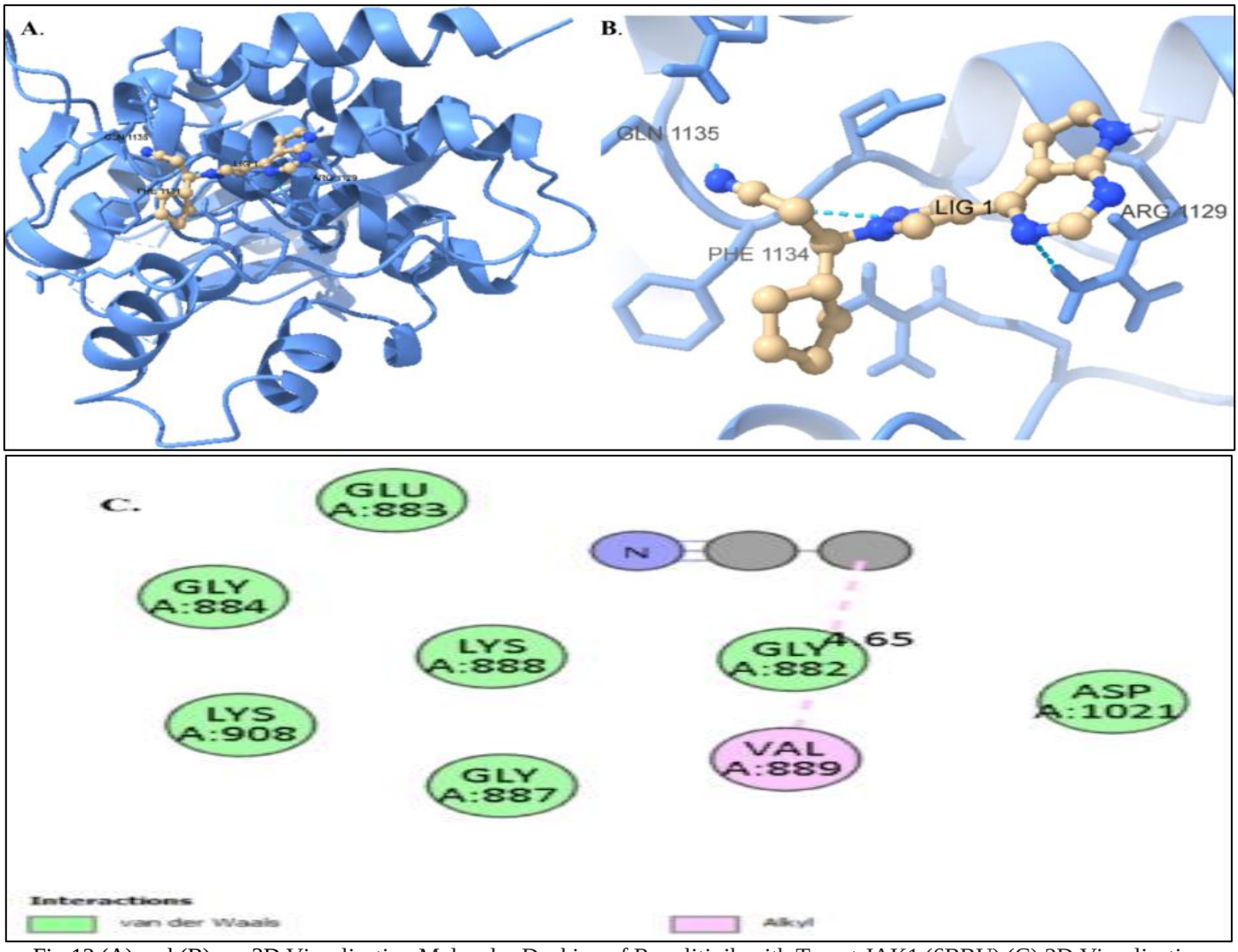

Fig 12 (A) and (B) are 3D Visualization Molecular Docking of Ruxolitinib with Target JAK1 (6BBU) (C) 2D Visualization Docking of Ruxolitinib with Target JAK1 (6BBU)

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Tofacitinib stably binds to the JAK1 active site (Figure 13) through hydrogen bonds with GLN904, PRO960, and SER961. Its binding energy (−7.02 kcal/mol) supports reported JAK1–Tofacitinib interactions, confirming its potential as an effective JAK1 inhibitor.

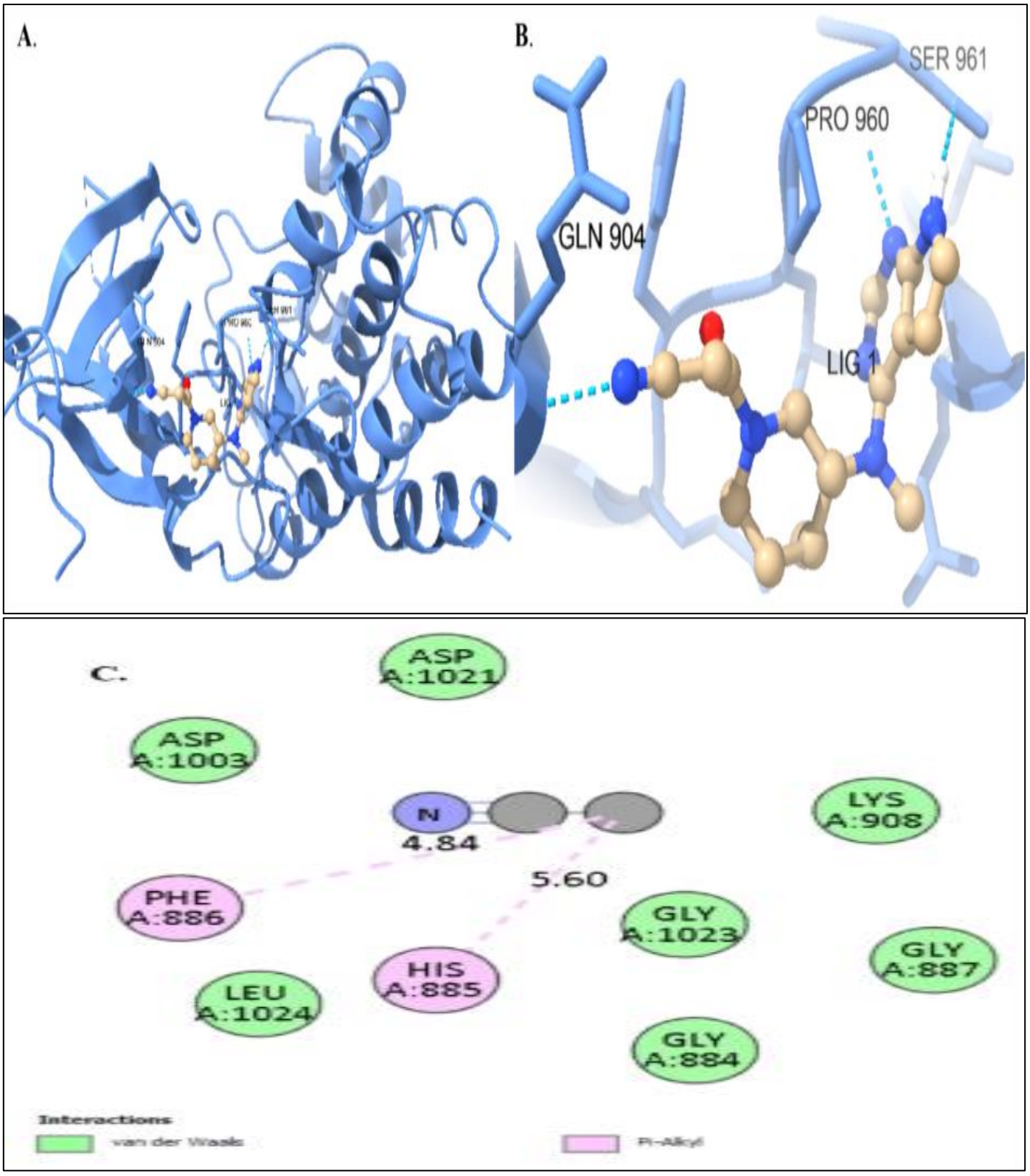

Fig 13 (A) and (B) are 3D Visualization Molecular Docking of Tofacitinib with Target JAK1 (6BBU) (C) 2D Visualization Docking of Tofacitinib with Target JAK1 (6BBU)

Baricitinib binds stably to the JAK2 active site (Figure 14) via a hydrogen bond with ARG975. Its binding energy (−7.69 kcal/mol) indicates strong affinity, confirming its potential as an effective JAK2 inhibitor.

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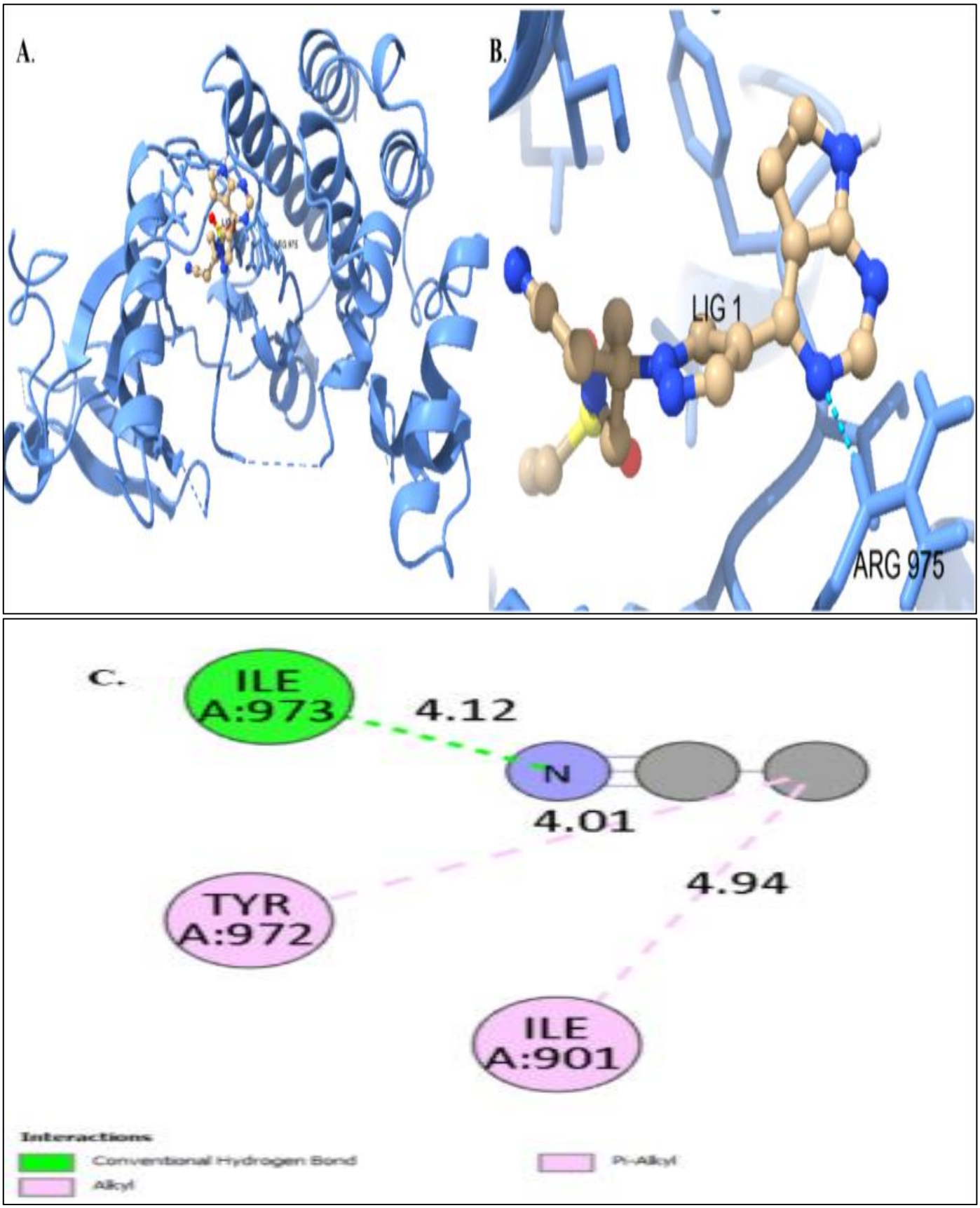

Fig 14 (A) and (B) are 3D Visualization Molecular Docking of Barcitinib with Target JAK2 (7RN6) (C) 2D Visualization Docking of Barcitinib with Target JAK2 (7RN6)

Fedratinib binds stably to the JAK2 active site (Figure 15) via a hydrogen bond with SER1054. Its strong binding energy (−9.44 kcal/mol) indicates high affinity, confirming its potential as a potent JAK2 inhibitor.

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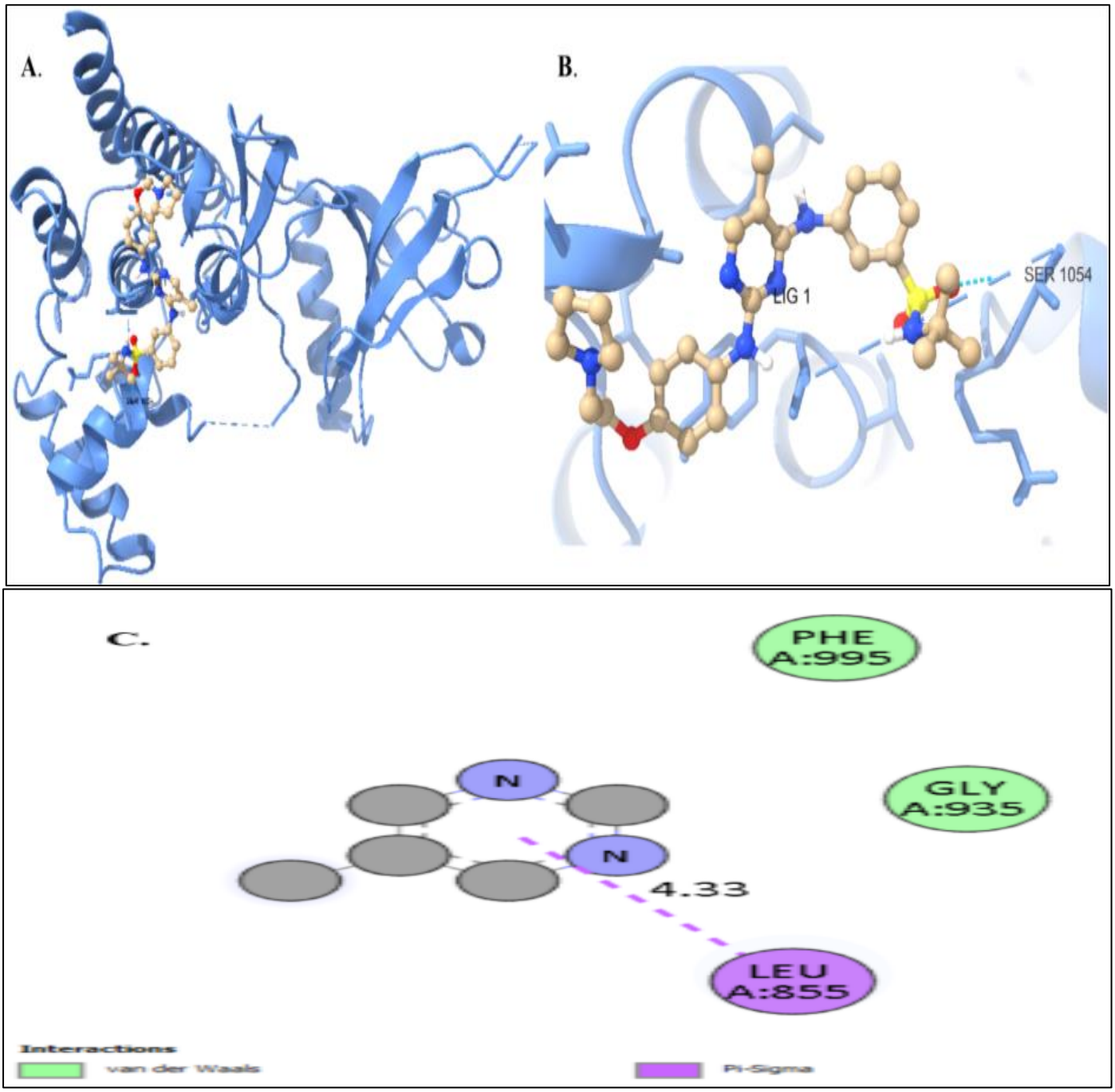

Fig 15 (A) and (B) are 3D Visualization Molecular Docking of Fedratinib with Target JAK2 (7RN6) (C) 2D Visualization Docking of Fedratinib with Target JAK2 (7RN6)

VIII. FUTURE PROSPECTIVES

Two computational methods that are becoming increasingly significant in the hunt for novel treatments for vitiligo are molecular docking and computer-aided drug design (CADD). Thanks to the growing availability of structural data for vitiligo-related targets, future research can employ high-throughput virtual screening to identify compounds that can modify proteins involved in melanocyte survival, immunological dysregulation, and oxidative stress pathways. By incorporating machine learning and artificial intelligence into docking algorithms, binding prediction accuracy can be increased and promising candidates can be quickly chosen.

Furthermore, by providing information on the stability and dynamic behavior of ligand-target complexes, combining free energy estimates with molecular dynamics simulations might improve docking studies. In silico ADMET profiling will reduce the likelihood of late-stage failure by facilitating early evaluation of pharmacokinetic properties and toxicity. Additionally, molecular docking-based drug repurposing methods might speed up the identification of presently approved drugs that might be useful in treating vitiligo, offering a shorter path to clinical application.[11]

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In the future, it will be possible to uncover new treatments more quickly, increase productivity, and increase their success rate by integrating these computational methods with experimental validation, such as melanocyte culture assays or skin models. As computer power and predictive algorithms continue to grow, these in silico techniques are expected to play a critical role in developing safe, effective, and personalized vitiligo therapies.[3]

IX. CONCLUSION

Fedratinib, Tofacitinib, Baricitinib, and Ruxolitinib have substantial binding affinities toward JAK1 and JAK2, important proteins involved in the immunological dysregulation leading vitiligo, according to molecular docking investigations in this paper. Among these, fedratinib showed the most beneficial interactions, suggesting that it may be the most promising choice for altering the JAK-STAT pathway and perhaps restoring melanocyte function. These findings imply that the drugs being studied may help vitiligo sufferers repigment, reduce skin inflammation, and prevent or diminish depigmentation.

This work shows how in silico screening can effectively find potential candidates prior to synthesis, saving time, money, and resources compared to traditional drug discovery. By integrating molecular docking with ADMET profiling and molecular dynamics simulations, these compounds' stability, safety, and drug-like properties may be further verified. Repurposing approved JAK inhibitors may also accelerate their clinical application, providing vitiligo sufferers with effective therapy more quickly. All things considered, this work highlights the significance of computational drug design in guiding experimental studies and encouraging the development of targeted, efficient, and potentially patient-specific vitiligo therapies.

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