Molecular Docking Analysis of Bioactive Compounds from Processed Plumbago zeylanica roots targeting Inflammatory Pathways in arthritis

Tanmoy Das

tdas92848@gmail.com

Dr B c roy college of pharmacy

Mrinmoy Das

Dr B c roy college of pharmacy

Research Article

Keywords:

Posted Date: June 2nd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9827651/v1

Additional Declarations: No competing interests reported.

Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by joint inflammation and cartilage degradation, necessitating safer and effective therapeutic agents. *P. zeylanica*, a medicinal plant used in traditional Ayurvedic medicine, exhibits promising anti-arthritic properties already highlightedin our previous studies. This study employed an integrated in-sillico approach combining network pharmacology and molecular docking to elucidate the probable anti-inflammatory mechanisms underlying the anti-arthritic effects of P. zeylanica. Key biological processes identified include responses to oxygen-containing compounds, organic and chemical stimuli, and pathways associated with cancer, PI3K/AKT signaling, lipid metabolism, microRNAs in cancer, calcium signaling, and fluid shear stress in atherosclerosis. Protein-protein interaction network analysis highlighted pivotal targets such as mTOR, PIK3CA, AKT1, MAPK1, JAK2, and MMP9. Molecular docking revealed strong binding affinities of major phytoconstituents like lumbagic acid, zeylenone. lupeol and others with these targets, demonstrating favorable physicochemical properties and stable interactions. These findings suggest that P. zeylanica modulates multiple inflammatory and signaling pathways relevant to arthritis pathogenesis. However, as this study is computational, experimental validation through *in-vitro*, *in-vivo* studies is essential to confirm these mechanisms and support future therapeutic development. This work provides a systematic biological framework for understanding the multi-target anti-arthritic potential of P. zeylanica and guides further experimental exploration.

1. Introduction

Arthritis is an autoimmune chronic inflammatory disorder of joints. It is a prototype of such illness resulting in destruction of articular and periarticular structure[25]. It is characterized by T-cell-mediated disease, with the increase of T cells and macrophages and fibroblasts, responsible for the destructive changes in joints. This immune-mediated inflammatory sinusitis, which leads to hyperplasia, cartilage destruction, bone erosion joint deformities (26). According to the epidemiology the prevalence of disease is 0.3-1% prone to women rather than men (25), that afflicts 1–2% of the global population. The origin of this disease is usually ranging aged between 35–60. It can also effects in young children even below age 16 that is referred to as juvenile rheumatoid arthritis (JRA). The systemic complications of arthritis are pericarditis, myocarditis, rheumatoid nodules, vasculitis, choroiditissjogrens syndrome, anxiety, depression, stress sicca syndrome, scleritis (27).Treatment of arthritis includes lifestyle modification, drug therapy, sclerotherapy, and surgery. DMARDs, NSAIDs, corticosteroids and TNF inhibitor are the current medications but this medications have thoughtful adverse effects and very expensive (28) .Diagnostic criteria of RA has moved from traditional strategies such as NSAIDS, corticosteroids, immunosuppressant's, DMARDS they are new to biological events such as TNF-a and monoclonal antibodies. The process made in the cure of disease, that treatment can't provide long term activity they show severe adverse side effects such as ulcer, renal morbidity, and cardiovascular issues, which limit their utility in the treatment of the disease. According to their treatment the side effects of recent treatment is cost effective so that very few patients have complications for musculoskeletal

disorders. Alternative medicines & complementary medicines are essential for those who are suffering from this disease.

A variety of medicines is advocated in Ayurveda to treat painful musculoskeletal disorders. *Plumbago zeylanica* L (family Plumbaginaceae)], is commonly known as Chitra and Chitramoolam. It is an important plant of the Ayurvedic system of medicine known as Chitraka, which consists of dried mature roots of P. zeylanica. The roots and root bark have high medicinal uses. They are bitter, stomachic, carminative, anthelmintic, astringent, cure intestinal troubles, dysentery, inflammation, piles, bronchitis, constipation, rheumatic diseases, and skin diseases. The root extract exhibited CNS stimulatory activities [32] hypolipidemic effect (Ram, 1996), anti-tumor, antimicrobial, anticancer, and wound healing activities. The major phytoconstituents of the root include plumbagin, 3- chloroplumbagin, elliptinone, chitranone, zeylinone, isozeylinone, droserone, plubagic acid, plumbazeylinone, naphthalene, and isoshinanolone [31].Sankaram and Siddhu, 1971). As per Ayurvedic texts, the P. zeylanica roots are subjected to Shodhana process before their use to reduce their toxic manifestations (Ayurvedic Pharmacopoeia of India, 2000). The purified roots are widely used in Ayurveda for the treatment of Sotha (inflammatory disease), Arsa (piles), GrahaniRoga disorder like gastric ulcer and Gudasotha (inflammation of the rectum). The important Ayurvedic formulations of Chitraka used for gastrointestinal diseases are Chitrakadivati, Chitrakadiharitaki, and Chitrakadichurna [Ayurvedic Pharmacopoeia of India, 2000; Database on Medicinal Plants in Ayurveda, 2000]. Previous studies revealed the anti-inflammatory activity of P. zeylanica [35].In our preliminary work the purified roots *P. zeylanica* methanolic extract was found to be potent. The methanolic extract of the purified root was found to have the highest anti-inflammatory activities [5]. This study is employed an integrated in-sillico approach combining molecular docking to elucidate the probable anti-inflammatory mechanisms underlying the anti-arthritic effects of P. zeylanica.

2. Materials and methods

2.1. Molecular docking studies

2.1. 1.PPI network-based collection of potential RA targets

DisGeNET (https://www.disgenet.org) is used to grab the information about genes and variants related to human diseases Search for disease keyword “Rheumatoid Arthritis” was made in the DisGeNET, GeneCards databases to download the RA target information [3]. The genes included in this PPI network were selected based on their well-established roles in the inflammatory, immune, and degenerative pathways associated with arthritis. Both rheumatoid arthritis (RA) and osteoarthritis (OA) involve complex gene networks that regulate cytokine production, immune cell signaling, joint destruction, and systemic inflammation. The chosen genes represent hub nodes and key regulators in these interconnected pathways. To build a Protein-Protein Interaction (PPI) network,the selected targets were instigated into the STRING 11.0 database (Swiss Institute of Bioinformatics, Switzerland,https://string-db.org/) with ‘*Homo sapiens*’ selected as species and a threshold of ‘highest confidence > 0.8’ for

minimum interaction[2]. These networks were also visualized using Cytoscape_v3.10.3 (https://cytoscape.org/) with that 13 common genes are specified.

2. 1.2.Preparation of proteins for docking analysis

The corresponding gene targets were identified by using Uniprot (http://www.uniprot.org/).The corresponding protein subtype PDB ID was obtained through the RCSB (http://www.rcsb.org) website[5]. Simultaneously, the latest functional proteins that complexed with ligands were obtained and then viewed by Discovery Studio Visualizer to determine the binding sites Therefore, six protein targets were identified as acceptors for molecular docking, including PI3K-γ ,IL-6 IL-2 TNF-α COX-2 VEGF. In this regard, the molecular docking of small molecules identified from LCMS was subjected against different protein targets using AutoDock Vina(version 1.5.7, latest available)[6]. Later the molecule possessing the best binding affinity was subjected to molecular dynamics simulation. The three dimensional structures of the ligands were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Each ligand was docked against the Hub genes using AutoDock Vina (https://vina.scripps.edu/) Following the docking process, the ligand poses with the lowest binding energy was chosen for visualization of ligand-protein interactions using Discovery Studio 2021.

2.1.3. Sources for preparation of candidate chemical component ligands
The LC–MS chromatogram of the PZME was represented in our previous studies. which revealed the presence of taraxasterol, α-amyrin, β-amyrin, calendol, saponaretin, N-(N'-benzoyl-S-phenylalaninyl)-S-phenylalaninol, apigenin-7-β-rutinoside, friedelinol, plumbagic acid, docosanoic acid methyl ester, acrimarine H, 4,4 difluro-17- beta-17 beta-hydroxy-17alpha-methyl-androstan-5-en-3-one, 1H-indole-2-carboxylic acid, 6-(4-ethoxyphenyl)-3-methyl-4-oxo-4,5,6,7-tetrahydro-isopropyl ester, β-sitosteryl glucoside, β-sitosterol, stigmasterol acetate, lupeol acetate, heneicosanoic acid, methyl ester, zeylanone, isozeylanone, elliptinone, plumbagine K, 1-keto-3β,19α-ainyaroxyurs-12-ene-24,28-dioic acid dimethyl ester, quercetin 3-o-neohesperidoside, nonyl 8-methyl-dodec-7-enoate, gugulterol-18-ferrulate, 3,3-biplumbagin, chitranone, maritinone and isoorientin in PZME.The 3D structure of the bioactive compounds identified from LCMS profiling were downloaded from the PubChem Database in SDF format[1].Then the energy minimized ligands were converted into PDBQT format using PyRx v.0.8 and the files were used for docking analysis[2]

3. Results

3.1. Molecular docking analysis

3.1.1. Rheumatoid Arthritis Targets and PPI Network Analysis

The next step was generating the network between the compounds (phytoconstituents obtained from the DisGeNET and from the generated network, finding the notable target proteins. The network generated in Cytoscape_v3.10.3 The most notable RA-linked genes (these genes were found using the frequency of repetition) were *MAPK1,AKT1*, *IL6*, *JAK2*, PTGS2, HLA-DRB1,TP53,RELA and IFNG. The network of the target proteins related to *P. zeylanica* and RA in Cytoscape software (Fig. 1) showed that there were 430 mutual genes between top 13 phytoconstituents-related and RA-linked targets are specified.

3.1.2. Binding Scores of protein targets with ligand

*Here t*he top compound based on the binding energies/docking scores *are chosen for protein-ligand interactions. This complexex is specified in the* **Table no:1**. *While*, HUMAN INTERLEUKIN-6 (PDB ID: 1ALU) were found to be Apigenin-7-β-rutinoside (-8.4 kcal/mol).In case of Apigenin-7-β-rutinoside. It was found to be three conventional hydrogen bonds with ARG A: 179, ARG A: 182, GLN A: 175. Crystal structure of TNF-α with a small molecule inhibitor (PDB ID: 2AZ5) were found to be Friedelinol (-9.5 kcal/mol). In case of Friedelinol it was found to form one pi-alkyl interaction with LEU A: 57. Crystal Structure of Indomethacin-(S)-alpha-ethyl-ethanolamide bound to Cyclooxygenase-1 (PDB ID: 2OYU) were found to be Friedelinol (-9.2 kcal/mol). In case of Friedelinol, it formed covalent bond with ASN P: 968. Human IL-2 Complexed with (R)-N-[2-[1-(Aminoiminomethyl)-3-piperidinyl]-1-oxoethyl]-4-(phenylethynyl)-L-phenylalanine methyl ester (PDB ID: 1M48) were found to be Apigenin-7-β-rutinoside (-8.4 kcal/mol). In case of Apigenin-7-β-rutinoside, it formed pi-pi T-shaped interaction with PHE A:42 residues, while it was found to form four pi-alkyl interaction with ARG A:38,ALA A:73, LYS A:35 and LEU A:72 residues. KDR in complex with ligand lenvatinib (PDB ID: 3WZD) were found to be Friedelinol (-9.2 kcal/mol). In case of Friedelinol, it formed pi-Sigma bond with LEU A :840,While it was found to form pi-Sulfur bond with CYS A:1045,It was found to be seven Pi-Alkyl bonds with VAL A:916, LEU A:1049,VAL A:848,LYS A:868,PHE A: 1047 LEU A: 889,PHE A:918 **.** The Jak1 kinase domain in complex with compound 37 (PDB ID: 4K6Z) were found to be Apigenin-7-β-rutinoside (-9.2 kcal/mol). In case of Apigenin-7-β-rutinoside, It was found to be two Pi-Alkyl bonds with CYS A: 106, ILE A:214. It was found to be Pi-sulfur bonds with Glu A: 192, ASP A: 241 **.** PI3K gamma in complex with 1-[6-(5-methoxypyridin-3-yl)-1,3-benzothiazol-2-yl]-3-[2-(1-propyl-1H-imidazol-4-yl)ethyl]urea(PDB ID: 4PS3) were found to be Zeylanone (-10.8 kcal/mol). In case of Zeylanone, It was found to be two Pi-sulfur bonds with MET A: 938, TRP A: 812.While it was found to form one Pi-sigma bond with ILE A:879. It was found to be four Pi-alkyl bonds with ILE A: 881, ILE A: 963, PRO A:810, ILE A :831. Crystal structure of human SMYD3 in complex with a VEGFR1 peptide (PDB ID: 5EX3) were found to be Friedelinol (-8.4 kcal/mol). In case of Apigenin-7-β-rutinoside It was found to be three conventional hydrogen bonds with ARG A: 179, ARG A: 182, GLN A:17

Table 1
Binding scores of phytoconstituents of PZME with RA-targets

SL NO.	LIGANDS	PDB ID: 1ALU	PDB ID: 2OYU	PDB ID: 1M48	PDB ID: 3WZD	PDB ID: 5EX3	PDB ID: 2AZ5	PDB ID: 4PS3	PDB ID: 4K6Z
1	Friedelinol	-8.3	**-9.2**	**-9.6**	**-8.7**	**-9.3**	-8.3	-9.9	-7.6
2	Plumbagine K	-7.6-	-7.2	-6.1	-6	-6.2	-6.4	-7.6	-6
3	Isoorientin	-6.7	-7.7	-8.3	-8.2	-8.1	-9.4	-7.3	-6.7
4	Docosanoic acid, methyl ester	-5.6	-5.4	-5	-4.3	-4.1	-4.6	-5.3	-4.5
5	Apigenin-7-β-rutinoside	**-8.4**	-9	-6.2	-8.4	-8.8	-8.2	-10.5	**-8.2**
6	Lupeol	-7	-7.8	-9.2	-7.5	-8.3	**-9.5**	-9	-7.3
7	Heneicosanoic acid, methyl ester	-4.1	-5.2	-5.1	-4.4	-4.5	-4.4	-5.8	-3.9
8	Stigmasterol Acetate	-7.5	-7.8	-8.1	-7.3	-7.7	-7.1	-9.1	-7.5
9	α-Amyrin	-6.7	-7.3	-8.7	-8.1	-7.9	-8.1	-9.5	-7.6
10	β-Amyrin	-7.5	-8.6	-8.8	-8.4	-8.6	-7.8	-10	-7.9
11	Lupeol Acetate	--8.2	-8.2	-8.9	-7.60	-7.9	-7.7	-7.3	-7.2
12	Quercetin 3-O-neohesperidoside	-7.5	-7.8	-8.2	-7.5	-7.3	-8	-9.8	-6.9
13	Zeylanone	-7.6	-8.6	-9.1	-8.6	-8.2	-8.6	**-10.8**	-7.8
14	Isozeylanone	-7.3		-8.1	-8.4	-8.5	-9.4	-8.7	-7.9
15	Elliptinone	-7.6	-8.1	-8.4	-7.9	-6.8	-7.8	-7.5	-7.3
16	6-(4-ethoxyphenyl)-3-methyl-4-oxo-4,5,6,7-tetrahydro-isopropyl ester	-7.6	-7.4	-7.3	-7.1	-6.4	-7.6	-7.4	-7.4
17	1H-Indole-2-carboxylic acid	-8.1	-7.5	-7.6	-6.4	-6..8	-8.1	-7.6	-7.5

Table 2
Overview of ligands interact with RA-Targets

Target	Key Interactions	Hydrogen Bonds	Water Bridges	Hydrophobic Contacts	Binding Pocket Fit
PI3K gamma	ARG, PHE, GLN, ASP	Multiple	Few	Several	Snug
IL-6	HOH, PRO, MET, GLY, LEU	Multiple	Several	Some	Well-fitted
IL-2	MET, LEU, VAL	Few	None	Several	Less extensive
TNF-alpha	CYS, TYR, LEU, HIS	Few	None	Several	Moderate
COX	GLU, ASN, PRO, ARG, THR, ILE	One	None	Several	Good
VEGF	GLU, LYS, PHE, THR, ARG	One	None	Several	Well-fitted

4. Discussion

The molecular docking studies presented demonstrate the interaction of a bioactive ligand with several key protein targets involved in inflammation and angiogenesis, including TNF-α, COX, VEGF, PI3Kγ, IL-6, and IL-2. The overview of ligands-protein interactions already demonstrated in the **Table no:2.** The results of thr interactions are demonstrated on [table no:.2]The results provide insights into the binding affinity and molecular basis of interaction, suggesting potential inhibitory effects of the ligand on these targets. The ligand binds deeply within the TNF-α binding pocket, forming several hydrophobic interactions with residues such as TYR C151, ILE C155, and LEU C57 **[Fig no:.3B]**. Notably, a π-π stacking interaction appears with TYR C151, enhancing the binding stability. The 3D visualization shows the ligand well accommodated in the binding cleft, indicating a favorable fit. This suggests the ligand could act as a TNF-α inhibitor, potentially reducing pro-inflammatory signaling. The ligand interacts predominantly with GLU P377 via hydrogen bonding, alongside hydrophobic contacts with PHE P371, ASN P122, and GLN P44**[Fig no:.3C]**. The orientation within the binding site mirrors typical NSAID binding modes. The 3D visualization reveals good surface complementarity, implying that the ligand may inhibit COX activity and thus reduce prostaglandin synthesis and inflammation. Hydrogen bonding with GLU A850 and proximity to residues like PHE A918 and LYS A920 suggest moderate interaction with the VEGF receptor**[Fig no:.3F]**. While not as deeply embedded as in TNF-α or COX, the ligand occupies a critical part of the receptor interface. This interaction could interfere with VEGF signaling and angiogenesis, making it relevant for anti-cancer or anti-angiogenic therapy. PI3Kγ binding displays the most complex interaction pattern, with multiple hydrogen bonds and hydrophobic contacts, especially involving ARG A849, PHE A698, TYR A787, and ASP A654**[Fig no:.3E]**. This rich interaction profile, especially the electrostatic complementarity observed in the 3D structure, suggests a strong binding

affinity. Inhibition of PI3Kγ is significant in modulating immune cell function and inflammation.The interaction is primarily water-mediated, as seen in the hydrogen bonds with several water molecules and surrounding residues such as PRO D.70, MET C.392, and GLY C.367. Though indirect, the presence of bridging water molecules supports ligand stabilization within the IL-6 interface **[Fig no:.3A]**. Such interactions could allosterically affect IL-6 binding to its receptor, potentially attenuating cytokine signaling. The ligand interacts with MET A:23 and forms hydrogen bonds with residues including VAL B:91. The binding is comparatively simpler, but the involvement of key surface residues suggests the potential to interfere with IL-2 receptor signaling **[Fig no:.3G]**. Given IL-2's role in T-cell proliferation, this could have immunomodulatory implications. Notably processed p.zeylanica phytoconstituents are greatful to find arthritis mechanism.

5. Conclusion

This study explores anti-arthritic actions of processed Plumbago zeylanica, focusing on its bioactive compounds and their interactions through computational analysis. this approaches proves that central targets like PIK3CA, AKT1, MAPK1, JAK2,IL-1,IL-6 that exhibited by strong binding affinity of p.zeylanica and their favorable physicochemical properties. The findings highlight a roadmap for future research to translate computational insights into therapeutic strategies for arthritis. The docking results collectively suggest that the ligand possesses multi-target binding potential, with the strongest predicted interactions observed with **TNF-α**, **PI3Kγ**, and **COX**, all of which are central players in inflammation. The ligand’s capability to also interact with **VEGF**, **IL-6**, and **IL-2** points toward a broader pharmacological profile that could be exploited in treating complex inflammatory or immune-related diseases, including cancer and autoimmune disorders. The next study to find out the long term in-vivo assessment of PZME.

Declarations

Funding

There is no funding for this research

Author Contribution

Author no 1 as mentioned prepare all the visual analysis manuscript preparation and interpretation of the findings Author 2 prepare all the diagrams and review the drafts of manuscript

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Figures

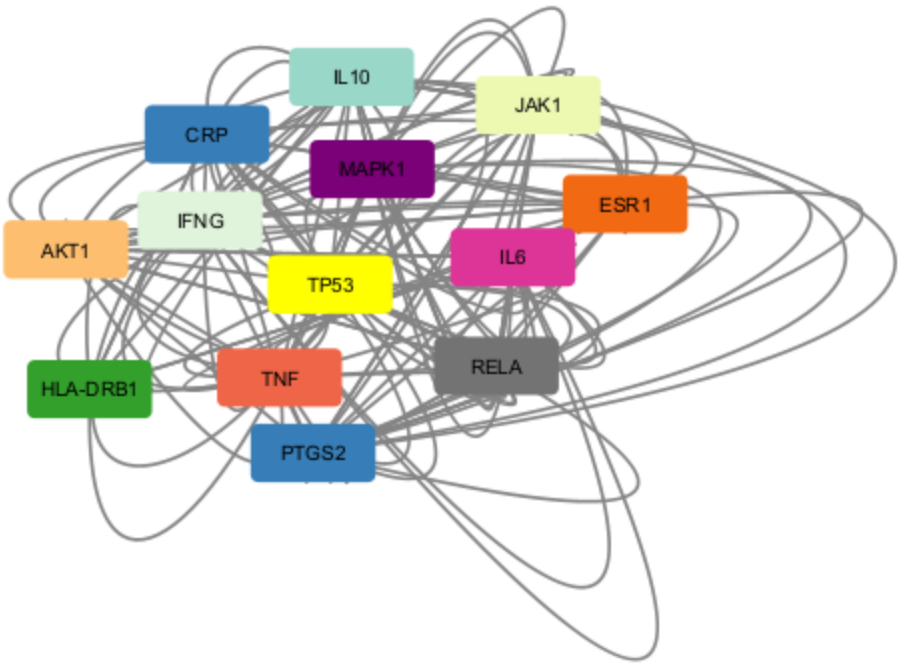

Figure 1

The PPI network based targets between rheumatoid arthritis (RA) and *P. zeylanica*.

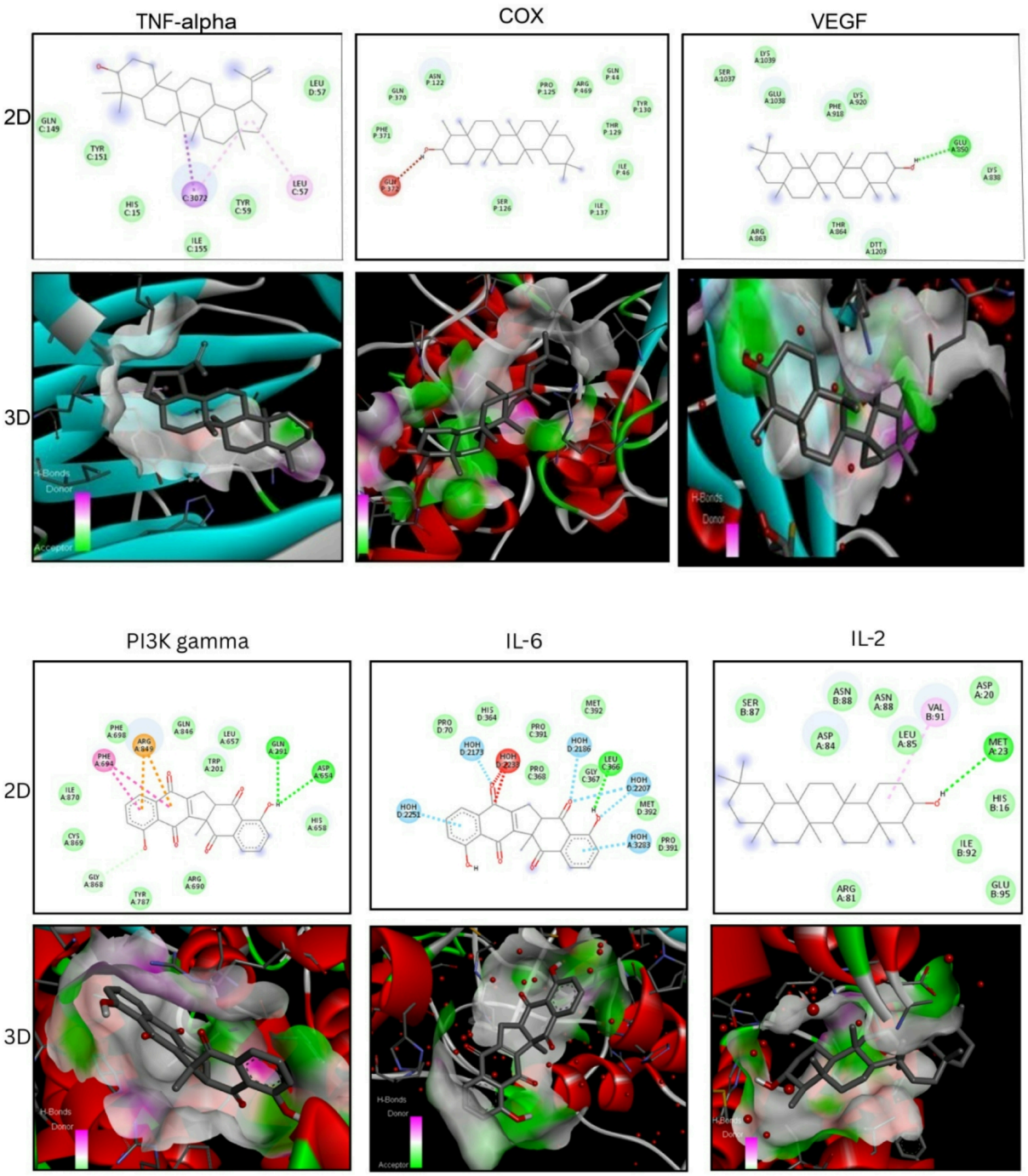

Figure 2

2d and 3d diagram of docking analysis of RA targets

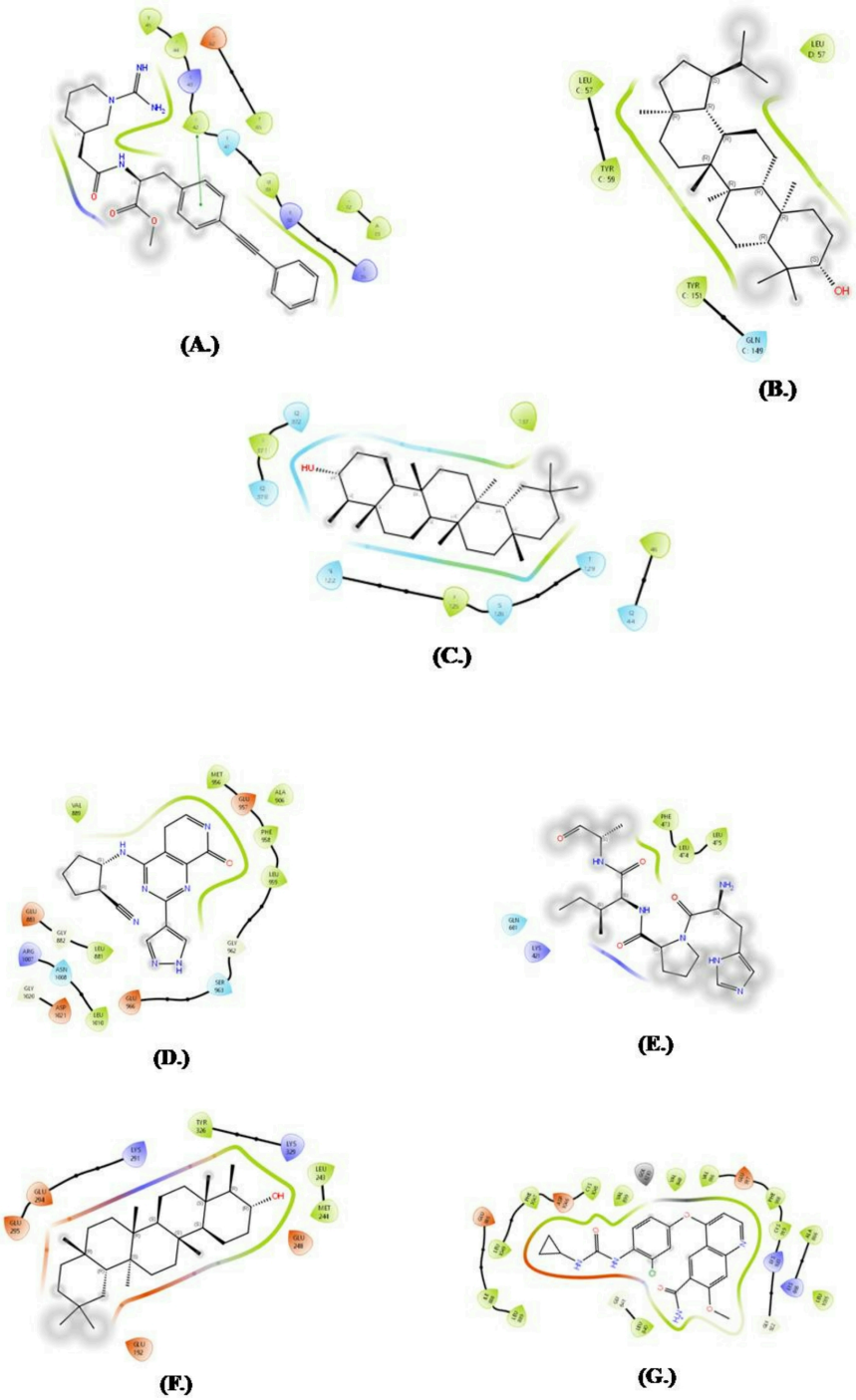

Figure 3

2D interactions and docking of ligand-RA targets