RESEARCH PAPER

Deciphering The Pharmacological Effects Of Raphanus Sativus L. In Rheumatoid Arthritis Through Network Pharmacology And Molecular Docking

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent joint inflammation and systemic consequences. Due to the limitations of conventional therapeutic approaches, natural alternatives with anti-inflammatory and immunomodulatory properties are being explored. *Raphanus sativus* L. (*R. sativus*), a medicinal plant rich in bioactive compounds such as terpenes, glucosinolates, and flavonoids, holds potential as a treatment for RA. This study employs molecular docking and network pharmacology to investigate the therapeutic potential of *R. sativus* in RA. RA-related genes and *R. sativus* phytochemicals were analysed to identify overlapping targets. Molecular docking studies were conducted to assess interactions between key phytochemicals and inflammatory receptors. ADMET analysis was performed to evaluate pharmacokinetic properties. A total of 166 overlapping targets were identified between RA-related genes and *R. sativus* phytochemicals, suggesting a multi-targeted therapeutic approach. Molecular docking revealed strong interactions between key compounds quercetin, lutein, and violaxanthin and TREM-1, a crucial receptor in inflammatory pathways. ADMET analysis confirmed favorable pharmacokinetic properties, though variations in toxicity and absorption require further investigation. While in silico results highlight *R. sativus* as a promising plant-based therapy for RA, further in vivo and clinical studies are necessary to confirm its safety and efficacy.

Key words: *Raphanus sativus L.*, rheumatoid arthritis, molecular docking, network pharmacology.

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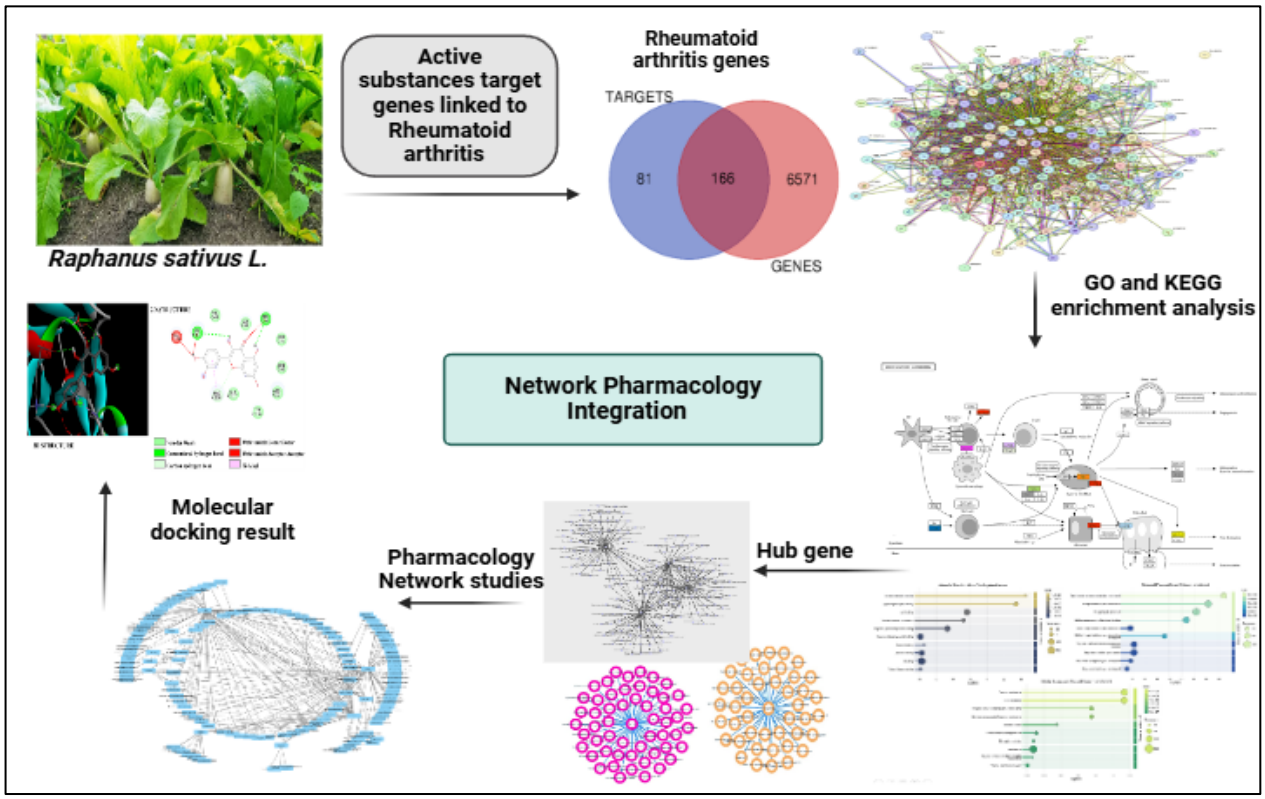
Graphical Abstract



1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation, cartilage degradation, and joint destruction (1). Approximately 70% of RA patients are female, and 55% are over the age of 55. RA is a significant contributor to disability and the global healthcare burden. According to the World Health Organization (WHO), RA commonly affects joints such as the elbows, shoulders, knees, ankles, wrists, hands, and feet (2). As of 2020, the global age-standardized prevalence of RA was 208.8 cases per 100,000 people, with an estimated 17.6 million individuals living with RA—a 14.1% increase from 1990. This number is projected to rise to 31.7 million by 2050 (3). Common clinical symptoms include morning stiffness, fatigue, fever, malaise, weight loss, pain in the neck, shoulder, and pelvic girdle, and the presence of rheumatoid nodules (4). Although the exact cause of RA remains unknown, it is driven by an autoimmune response targeting the synovial membrane of joints, leading to chronic inflammation, disability, and increased mortality (5). RA development involves both genetic predispositions and environmental triggers. During the preclinical phase, these factors initiate autoimmunity, marked by the production of anti-cyclic citrullinated peptide (anti-CCP) antibodies and rheumatoid factor (RF), even before symptoms appear (6). Clinical manifestations may vary from mild to severe, and disease progression can be unpredictable. Variations in the expression of inflammatory molecules and genetic markers contribute to the heterogeneity in disease progression among patients (7,8). Triggering Receptor Expressed on Myeloid Cells (TREM) proteins are a family of cell-surface receptors primarily expressed on myeloid cells like neutrophils, macrophages, and dendritic cells. They play key roles in innate immunity, inflammation, and tissue homeostasis (9). Among them, TREM-1 and TREM-2 are involved in modulating inflammatory responses and are found on both immune and non-immune cells (10). TREM-1, a member of the immunoglobulin superfamily, is associated with the ITAM-containing adaptor molecule DAP12 and is predominantly expressed on monocytes/macrophages and neutrophils. Its expression is enhanced by pro-inflammatory stimuli such as tumor necrosis factor (TNF) and toll-like receptor (TLR) ligands like lipoteichoic acid and lipopolysaccharide (11,12). TREM-1 is largely implicated in acute inflammatory responses, and its natural ligand remains unidentified (13). Activation of TREM-1 enhances the release of inflammatory cytokines and chemokines and upregulates cell-surface molecules associated with

immune cell activation and migration. *Raphanus sativus*, commonly known as radish, belongs to the Brassicaceae family and is widely consumed for its nutritional and medicinal properties (14). Its roots, seeds, and leaves exhibit diverse pharmacological activities. The color of its roots, ranging from red to purple, is attributed to anthocyanins such as pelargonidin and cyanidin. Different cultivars like daikon and mooli vary in size and shape and are often consumed raw or cooked. The phytochemical composition of *R. sativus* has been extensively profiled (15). However, to date, there are no reports investigating the interaction of *R. sativus* phytocompounds with TREM-1 in the context of RA.This study presents the first report exploring the anti-rheumatoid potential of *R. sativus* by targeting the TREM-1 receptor. We utilized in-silico tools including ADMET analysis, drug-likeness prediction, toxicity assessment, PASS prediction, Swiss target prediction, network pharmacology, and molecular docking to evaluate the potential of *R. sativus* constituents against RA.

Table 1: Phyto-constituents present in *R. sativus*

S.no	phytochemical	Percentage (%)
1	Flavonoids	38.8%
2	Non-flavonoids poly-phenols	8.4%
3	Terpenes and derivatives	8.2%
4	Fat and related fatty	6.4%
5	Aldehyde and ketones	3.6%
6	Glucosinolates and breakdown products	5.6%
7	Hydrocarbons	4.6%
8	Carboxylic acid	3.8%
9	Heterocyclic	3.6%
10	Other compounds	2.6%

2.MATERIALS AND METHODS

2.1. Data Retrieval

This work used target mining approaches in conjunction with internet resources such as String DB (v12.0) (16) and Swiss target prediction to identify the molecular targets impacted by *R. sativus* phytoconstituents and genes associated with RA. Potential anti-RA genes were identified by locating the intersection of these two sets of targets through Venplot databases. Subsequent analyses focused on Genecards networks (17), KEGG pathways (18), OMIM pathways, and Gene Ontology (GO)(19) to investigate the features of prospective targets. Furthermore, the study looked at the expression patterns of important genes related with RA. Finally, molecular docking techniques were used to assess the interaction of important genes discovered during the protein-ligand interactions study.

2.2. Screening

2.2.1. Drug-likeness analysis

Lipinski's rule of five (RO5) was used to evaluate the drug-likeness of putative medicinal substances utilizing a variety of characteristics. These parameters include the molecular weight (MW), XLogP3 (water-octanol partition coefficient), hydrogen bond donor count, rotatable bond count, and hydrogen bond acceptor count. The plant R. sativus phytoconstituents SMILES format was received from the PubChem database and entered into the Molsoft server, a web-based tool used to analyze the drug-likeness of compounds.(20)

2.2.2. Evaluation Pharmacokinetic Properties and toxicity prediction of phytoconstituents

ADMET analysis predicts a compound's toxicity and pharmacokinetic properties—absorption, distribution, metabolism, excretion—using web-based tools. In this study, ADMETLAB 2.0 was used to assess parameters like $CACO_2$ and MDCK permeability, liver absorption, plasma protein binding, volume of distribution, BBB penetration, CYP450 interactions, clearance, half-life, and toxicity. This aids in evaluating drug-like potential of the compounds (21)

2.3. Swiss target prediction

2.3.1. Access to possible *Raphanus sativus* targets and RA targets

Phytoconstituent data for *R. sativus* were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) (Gamba et al., 2021), and their Canonical SMILES or SDF files were used in Swiss Target Prediction (http://www.swisstargetprediction.ch/) to identify potential targets. These targets were converted to gene names via UniProt, and duplicates were removed. RA-related genes were retrieved from GeneCards and OMIM using the keyword "RA, Rheumatoid arthritis," resulting in 116 unique genes. Common targets between *R. sativus* and RA were identified using an online Venn diagram tool for further analysis (22)

2.3.2. Cluster analysis

Cluster topology modules are densely connected segments of molecular complexes seen in massive networks of protein-protein interactions. One categorization method that finds connected regions with inherent patterns in a network is cluster analysis. In the created protein-protein interaction (PPI) network, the study employed cluster analysis and the

Molecular Complex Detection (MCODE) plug-in of Cytoscape to find densely connected regions. We then selected important cluster modules from this network. According to the criteria, the degree cutoff was set at 2, the K-core was set at 2, and the node score cutoff was set at 0.2.(23)

2.4. Molecular Docking

2.4.1. Ligand Preparation

A total of 48 phytochemicals from *Raphanus sativus* and standard anti-rheumatoid drugs were selected. Their 3D structures were retrieved from PubChem, optimized using the Universal Force Field (UFF), and converted to PDBQT format for docking simulations.

2.4.2. Protein Target Preparation

The crystal structure of the human TREM-1 receptor (PDB ID: 1Q8M) was obtained from the RCSB Protein Data Bank. Co-crystallized ligands and non-essential hydrogen atoms were removed, the structure was energy-minimized, appropriate charges were assigned, and the final structure was converted to PDBQT format using tools such as PyRx, ensuring readiness for docking simulations (Fig. 1).

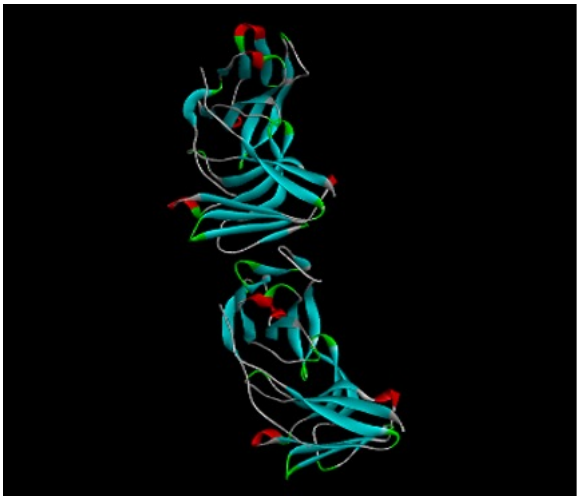


Fig. 1: Cleaned structure of Triggering receptor expressed on myeloid cells (TREM 1)

2.4.3. Target Functional Site Determination

Identifying the target protein's active site is crucial for docking analysis. CASTp (Computed Atlas for Surface Topography) is used to pinpoint amino acid residues forming the active pocket. This tool aids in visualizing the protein's surface, ensuring precise docking. A grid box is then created around the largest pocket, providing ample space for efficient ligand-protein interactions. (24,25).

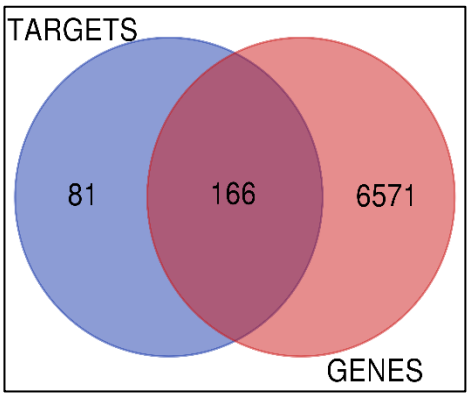
2.4.4. Protein-Ligand Interaction and Molecular Docking

48 compounds were chosen for the molecular docking investigation based on their anti-inflammatory qualities, and the docking engine was the AutoDock wizard in the PyRx program. The protein was seen to be firm during the docking procedure, but the ligands were regarded as adjustable. Using the binding amino acid analysis that was acquired via CASTp, the grid parameter configuration file was created. The ligand with the highest binding affinity was found to have the lowest (most negative) binding energy. Biovia Drug Discovery Studio, 2020, was used to visually analyse the docking site and protein-ligand interactions (26,27).

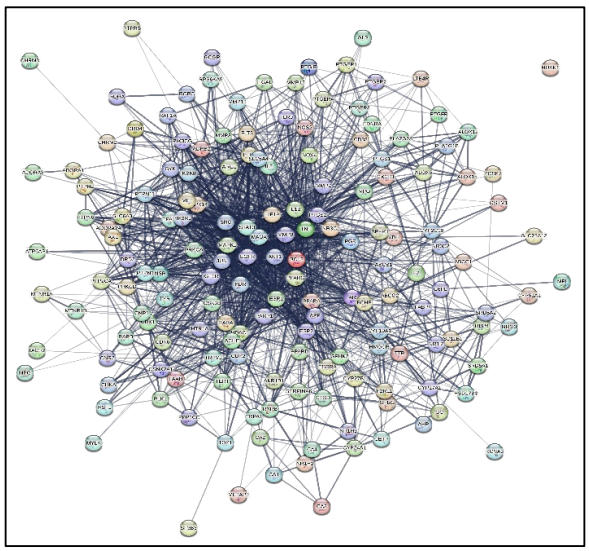
2.5. Results

2.5.1. Analysis between targets of *Raphanus sativus* and RA

The SWIZZ target prediction revealed 373 targets that were impacted by the actions of certain phytochemicals, including quercetin, β-carotene, lutein, and Violaxanthin. Additionally, a dataset of genes with differential expression was constructed using data from the OMIM database and Gene Cards. 373 chosen phytochemical targets, 6984 RA targets, and 166 common targets were matched for screening, according to the Venn diagram's results. *R. sativus* may be used to treat RA by targeting these 166 notable targets (**Fig. 2a**). They next created the Protein-Protein Interaction (PPI) network by entering the 166 targets into the STRING database (**Fig. 2b**). Additional analysis and visualization of the PPI network data using Cytoscape 3.9.0 revealed a network with 1755 edges and 165 nodes.



a)



b)

Fig. 2: Common overlapping 166 targets (a) Venn diagram of common targeted genes of *R. Sativus* in RA (b) STRING database

2.5.2. Arrangement and creation of a sickness goal network

The statistics were imported into Cytoscape to build the compound-target network, which allowed us to examine the signaling pathway and function of the selected target genes. The network of compound-goal-ailment interactions is built. It is made up of 166 interacting goal proteins and 4 parts. We found that numerous targets in this network had been struck by multiple components, as shown in (Fig. 3). This fact suggested that *R. sativus* active biochemistry may have a synergistic effect on those targets; in addition to RA, it has therapeutic effects on other illnesses and disorders. Cytoscape separate compound-target network of β-carotene, Violaxanthin, quercetin and lutein are shown in Fig 4.

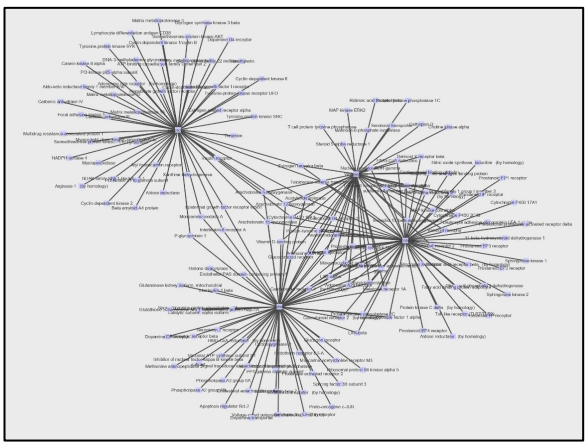


Fig. 3: Compound-targets network affected by common 166 genes

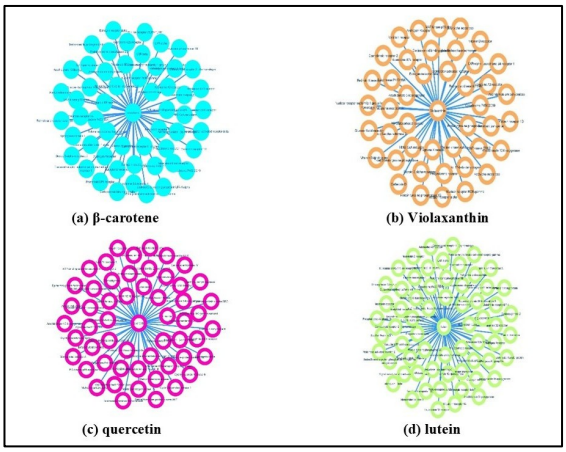


Fig. 4: Cytoscape compound-target network of (a) β-carotene (b) Violaxanthin (c) quercetin and (d) lutein

2.5.3. Results of GO and KEGG enrichment analysis

DAVID was used for GO and KEGG enrichment analysis on 166 potential targets of *R. sativus* phytochemicals against RA. GO analysis identified 853 enriched terms: 589 biological processes (BP), 69 cellular components (CC), and 195 molecular functions (MF). The top six terms from each category were visualized. Key biological processes included responses to chemicals, organic substances, oxygen-containing compounds, and multicellular processes Cellular components were mainly associated with the apical cell area, brush border, cell projection membrane, and actin-based projections (Fig. 5). Molecular functions were enriched in ion binding, nuclear receptor activity, and catalytic and protein kinase activity. KEGG pathway analysis revealed 10 key genes (fig.6). (e.g., MMP3, TNF, IL1, IL23A, JUN) involved in 436 pathways, notably RA, cancer, and inflammatory diseases like IBD (Fig. 7).

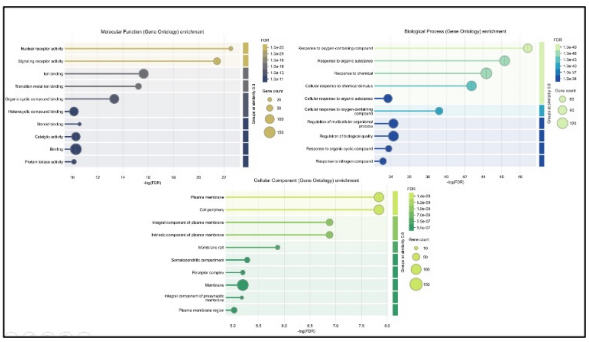


Fig. 5: Go enrichment analysis

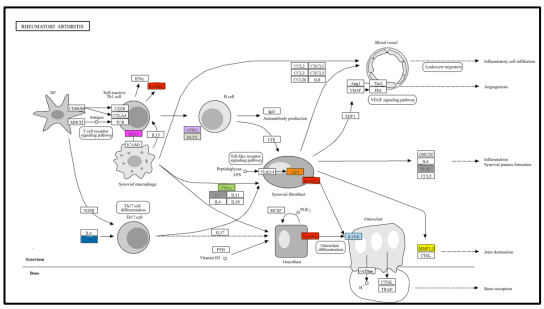


Fig.6: KEGG Pathway of RA - Color parts represent the targets of *R. sativus*

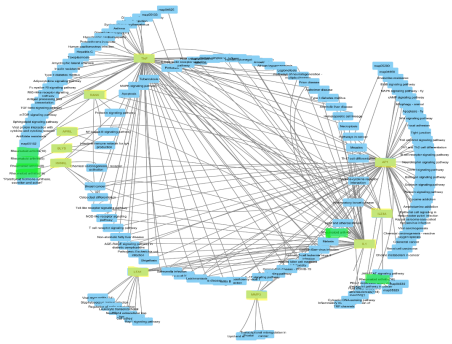


Fig. 7: Genes of *R. sativus* associated with various diseases

2.5.4. Cluster

The MCODE network analysis identified 5 clusters. Cluster 1, which had the highest score of 22.064, consisted of 155 nodes and 1721 edges. Cluster 2 comprised of 15 nodes connected by 33 edges (Fig. 8a). Cluster 3 comprised of 12 nodes, namely PCSK7, SRD5A2, HSD11B1, SERP1NA6, SHBG, SRD5A1, HSD17B3, CYP17A1, CYP51A1, CYP2A41, NR112, CYP27B1 connected by 23edges (Fig. 8b). Cluster 4 consisted of 11nodes, namelyATP6A1, PTPN2, SRD5A1, INSR, PTPN6, P1K3R1, PRKCD, PPP2CA, PPP1CC, RAP1A, AKR1B1with a total of 15edges (Fig. 8c) Cluster 5 consisted of nodes, namely CNR2, MTNR1B and MTNR1A, with a total of 3edges (Fig. 8d).

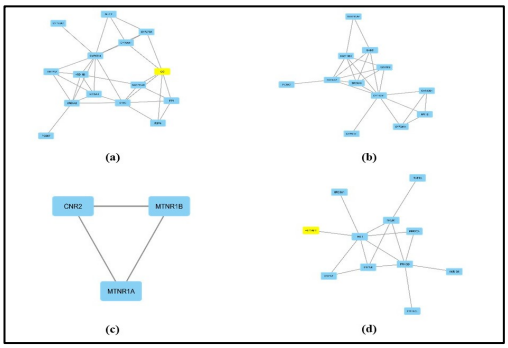


Fig. 8: (a, b, c, d): Cluster analysis

2.5.5. Determination Of Target Functional Site

The target protein Triggering receptor expressed on myeloid cells 1 (TREM 1) was used to analyse its functional binding sites using CastP. The amino acid molecules inside the protein's active pocket were also recognized by this instrument. The CastP results for the target protein's chains A, B, C, and D were shown in Fig. 9. Grid boxes were constructed to encompass the active protein's binding Site.

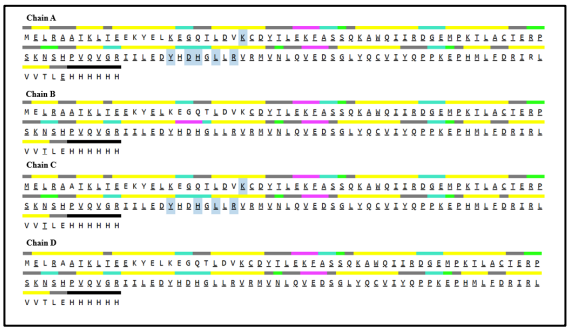


Fig. 9: The CASTp tool (Computed Atlas for Surface Topography) was used to identify active pocket-forming amino acid residues of the target protein. The largest binding pocket was observed at the active site, highlighted in blue.

2.5.6. Molecular Docking and The Analysis of Protein-Ligand Interactions

All 49 *R. sativus* phytochemicals were docked using PyRx against TREM-1 (PDB ID: 1Q8M, chains A–D). Compounds with binding affinities below -7 Kcal/mol were selected (Table 1), indicating strong ligand-receptor interactions. Five top compounds were analyzed further, and Table 2 details their interactions with key amino acid residues across protein chains A, B, and C. These interactions suggest potential binding stability and relevance in RA treatment, compared with standard drugs from NSAIDs, interleukin inhibitors, corticosteroids, DMARDs, and natural sources.

Table 2: Binding affinity of the Ligands towards receptor protein

S. No.	Ligands	Categories	Binding Affinity(K/mol)
1	Myricetin	*R. sativus* (flavonoid)	-6.3
2	Catechin	*R. sativus* (flavonoid)	-6.5

3	Epicatechin	*R. sativus* (flavonoid)	-6.7
4	Quercetin	*R. sativus* (flavonoid)	-7
5	4-vinyl-2-methoxyphenol (vinyl guaiacol)	*R. sativus* (non-flavonoid polyphenols)	-5
6	Foliar phenol	*R. sativus* (non-flavonoid polyphenols)	-4
7	Vanillic acid	*R. sativus* (non-flavonoid polyphenols)	-4.8
8	Sinapic acid	*R. sativus* (non-flavonoid polyphenols)	-4.9
9	p-coumaric acid	*R. sativus* (non-flavonoid polyphenols)	-5
10	Tyrosol	*R. sativus* (non-flavonoid polyphenols)	-5.3
11	Squalene	*R. sativus* (Terpenes and derivatives)	-4.6
12	β-carotene	*R. sativus* (Terpenes and derivatives)	-6.9
13	Lutein	*R. sativus* (Terpenes and derivatives)	-7.3
14	3- hydroxy-beta-ionone	*R. sativus* (Terpenes and derivatives)	-5.3
15	violaxanthin	*R. sativus* (Terpenes and derivatives)	-7.6
16	Carvone	*R. sativus* (Terpenes and derivatives)	-4.7
17	(E)-geranyl acetone	*R. sativus* (Terpenes and derivatives)	-4.1
18	camphene	*R. sativus* (Terpenes and derivatives)	-4.4
19	Piperiton	*R. sativus* (Terpenes and derivatives)	-6.3
20	Carvacrol	*R. sativus* (Terpenes and derivatives)	-5

21	Alpha-linolenic acid	*R. sativus* (Fat, fatty acids and related fatty compounds)	-4
22	Methyl palmitate	*R. sativus* (Fat, fatty acids and related fatty compounds)	-3.4
23	Palmitic acid	*R. sativus* (Fat, fatty acids and related fatty compounds)	-3.6
24	Oleic acid	*R. sativus* (Fat, fatty acids and related fatty compounds)	-3.7
25	Linolenic acid	*R. sativus* (Fat, fatty acids and related fatty compounds)	-4
26	Hexadecenoic acid(palmitic acid)	*R. sativus* (Fat, fatty acids and related fatty compounds)	-3.9
27	Methyl linolenate	*R. sativus* (Fat, fatty acids and related fatty compounds)	-4.7
28	(R)-4methylsulfinylbut-3-enylglucosinolate(glucoraphasatin)	*R. sativus* (Glucosinolates and breakdown products: Semi-synthetic chemical compound)	-5.4
29	4-methylthio-3-butenyl-glucosinolate (dehydroerucin or glucoraphasatin)	*R. sativus* (Glucosinolates and breakdown products: Semi-synthetic chemical compound)	-5.6
30	4-hydroxy-3-indolylmethyl glucosinolate(4-hydroxyglucobrassicin)	*R. sativus* (Glucosinolates and breakdown products: Semi-synthetic chemical compound)	-6.9
31	Methotrexate	Conventional synthetic DMADS	-6.7

32	Lethenomide	Conventional synthetic DMADS	-6.3
33	Sulfasalazine	Conventional synthetic DMADS	-5
34	Hydroxychloroquine	Conventional synthetic DMADS	-4.7
35	Totacitinile	Targeted synthetic DMADS	-5.6
36	Baricitinile	Targeted synthetic DMADS	-5.9
37	Upadacitinile	Targeted synthetic DMADS	-7.2
38	Tocilizumab	Interleukin Inhibitor	-5.6
39	Ibuprofen	Non – Steroidal Anti-Inflammatory Dmgs (NSAIDS)	-5.3
40	Naproxen	Non – Steroidal Anti-Inflammatory Dmgs (NSAIDS)	-6.3
41	Celecoxib	Non – Steroidal Anti-Inflammatory Dmgs (NSAIDS)	-6.6
42	Prednisone	Corticosteroids	-6.6
43	Methyl Prednisolone	Corticosteroids	-6.2

2.5.7. Ligand-Protein Interaction

Researchers used the Biovia Accellrys Discovery Studio Visualizer software to analyse the binding interactions between amino acid residues and the best-docked bioactive chemicals at their active sites. Protein-ligand interactions are mostly determined by the kind of bond, the quantity of hydrogen bonds, hydrophobic interactions, and binding affinity (Table 3) (Fig. 10, Fig. 11, Fig. 12, Fig.13 and Fig. 14).

Table 3: Protein-Ligand Interaction Analysis

Sl. No.	Ligands	No of Interaction	Amino acid Residues
1.	β-CAROTENE	5	A-CHAIN(VAL-101) C-CHAIN (ALA-68, CYS69, VAL-80, VAL-82)
2.	LUTEIN	7	A- CHAIN (MET-63, LYS-65, CYS-69, HIS-78, VAL-80, VAL-82) C-CHAIN (GLY-34)
3.	UPADACITINIB	9	C-CHAIN (LYS-47, PHE-48, GLN-52, ARG-72, PRO-73, TYR-116, GLN-117, PRO-118, GLU-121)
4.	VIOLOXANTHIN	5	A-CHAIN (SER-50, SER-51,

			PRO-118, PRO-119) B-CHAIN(ILE-57)
5.	QUERCITINE	4	C-CHAIN (LYS-47, SER-50, PRO-118, GLU-121)

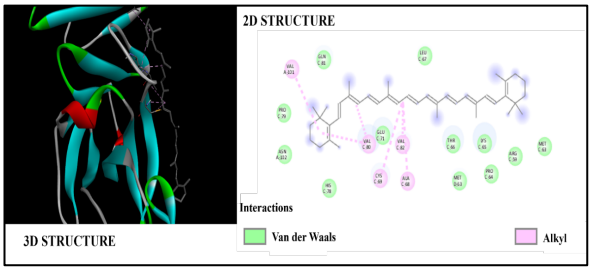


Fig. 10: Interaction of β-carotene on TREM-1

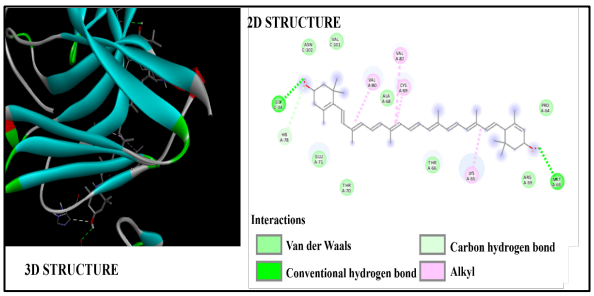


Fig. 11: Interaction of LUTEIN on TREM-1

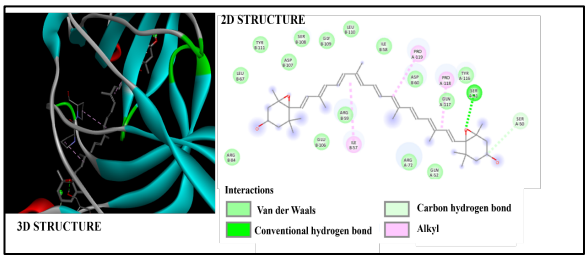


Fig. 12: Interaction of VIOLOXANTHIN on TREM-1

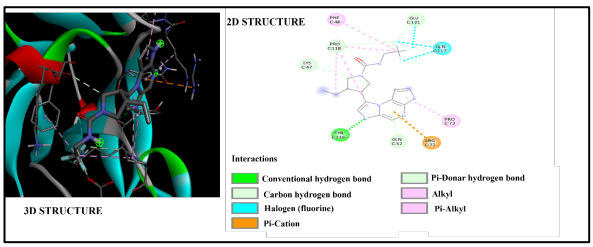


Fig. 13: Interaction of UPADACITINIB on TREM-1

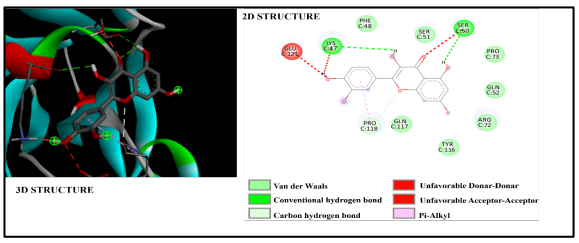


Fig. 14: Interaction of QUERCITINE on TREM-1

2.5.8. ADME Analysis

Table 4 presents a comparative pharmacokinetic analysis of five compounds—Violaxanthin, Lutein, Upadacitinib, Quercetin, and β-carotene—based on their absorption, distribution, metabolism, and excretion (ADME) profiles. In terms of absorption, all compounds showed low Caco2 permeability (negative values), with Upadacitinib exhibiting the highest (-4.888) and β-carotene the lowest (-5.469). Lutein had the highest MDCK permeability (1.7e-05), while Violaxanthin and β-carotene had the lowest (7e-06). Human intestinal absorption (HIA) was highest for Lutein and Quercetin (0.014), whereas Upadacitinib had the lowest (0.004), indicating limited intestinal uptake. Distribution data revealed that Violaxanthin and β-carotene had the highest plasma protein binding (PPB) at 105.8%, while Upadacitinib had the lowest (70.14%). Upadacitinib also demonstrated the highest volume of distribution (VD) at 1.313, and the highest blood-brain barrier (BBB) penetration (0.629), suggesting significant tissue and CNS distribution. The free fraction in plasma (Fu) was also highest for Upadacitinib (33.01%), followed by Quercetin (7.423%), and lowest for Violaxanthin and β-carotene (2.775%). Regarding metabolism, Violaxanthin, Lutein, β-carotene, and Upadacitinib were substrates of CYP2C9, suggesting metabolism via this pathway. Quercetin uniquely acted as an inhibitor of CYP1A2 (0.943) and CYP2C19 (-0.921), indicating potential for enzyme-related drug interactions. In terms of excretion, Quercetin showed the highest clearance (8.284), while Violaxanthin and β-carotene had the lowest (0.576). Upadacitinib had the longest half-life (0.422), indicating sustained presence in the system, while Violaxanthin and β-carotene exhibited the shortest half-lives (0.011), suggesting rapid elimination. Overall, Upadacitinib displayed strong distribution and metabolic stability despite low intestinal absorption, while Quercetin stood out for its rapid clearance and enzyme inhibition properties.

Table 4: Pharmacokinetic properties

SI.NO.	Property	Violaxanthin	Lutein	Upadacitinib	Quercetin	β-Ca

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ABSORPTION	Caco2 Permeability	-5.294	-5.379	-4.888	-5.204	-5.469
	MDCK Permeability	7e-06	1.7e-05	1.1e-05	8e-06	7e-06
	HIA	0.009	0.014	0.004	0.014	0.009
DISTRIBUTION	PPB	105.8%	102.1%	70.14%	95.49%	105.8%
	VD	1.175	1.19	1.313	0.579	1.175
	BBB Penetration	0.0	0.0	0.629	0.008	0.0
	Fu	2.775%	4.315%	33.01%	7.423%	2.775%
METABOLISM	CYP450 (High Metabolism)	CYP2C9 substrate-1.0	CYP2C9 substrate-1.0	CYP2C19 inhibitor-0.921	CYP1A2 inhibitor-0.943	CYP2C9 substrate-1.0
EXCRETION	CL	0.576	0.902	6.194	8.284	0.576
	T1/2	0.011	0.023	0.422	0.929	0.011

2.5.9. Toxicity Predictions

The toxicity profiles **(Table 5)** of the compounds were assessed based on their LD50 values, toxicity classification, and organ-specific toxicity. **Violaxanthin:** Moderate toxicity (LD50: 55 mg/kg) with respiratory toxicity. **Lutein:** High toxicity (LD50: 10 mg/kg) but no significant organ toxicity, except for potential immunotoxicity. **Upadacitinib:** Slight toxicity (LD50: 800 mg/kg) with respiratory and neurotoxicity. **Quercetin:** Moderate toxicity (LD50: 159 mg/kg) with respiratory and neurotoxicity. **β-carotene:** Slight toxicity (LD50: 1510 mg/kg) with neurotoxicity. Lutein exhibits the highest toxicity, while **β-carotene** and Upadacitinib show the lowest toxicity profiles. Respiratory and neurotoxicity are common among the compounds.

Table 5: Toxicity Prediction

S. NO.	LIGANDS	PREDICTED LD 50	TOXICITY CLASS	ORGAN TOXICITY
1.	Violaxathin	55mg/kg	3 (Moderate toxicity)	Respiratory Toxicity
2.	Lutein	10mg/kg	2 (High toxicity)	No Organ toxicity, shows immunotoxicity
3.	Upadacitinib	800mg/kg	4 (Slight toxicity)	Respiratory toxicity, Neurotoxicity
4.	Quercetin	159mg/kg	3 (Moderate toxicity)	Respiratory toxicity, Neurotoxicity
5.	β-Carotene	1510mg/kg	4 (Slight toxicity)	Neurotoxicity

2.6. Discussion

The research highlights the potential pharmacological advantages of *R. sativus* L. in the treatment of RA by using molecular docking and network pharmacology techniques. Systemic problems, cartilage degeneration, and chronic synovial inflammation are hallmarks of RA, a chronic inflammatory disease. Disease-modifying antirheumatic medications (DMARDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are two examples of conventional treatments that frequently cause side effects, making the search for safer and more efficient plant-based substitutes necessary. The bioactive components found in R. sativus, such as glucosinolates, terpenes, and flavonoids, have strong anti-inflammatory and immunomodulatory effects, according to our research. 166 common targets between R. sativus phytochemicals and RA-related genes were found via network pharmacology analysis, highlighting the plant's capacity to regulate important inflammatory processes. Important targets that are important mediators of RA pathogenesis, including TNF, IL1,

IL23A, and JUN, were identified using the protein-protein interaction (PPI) network. Triggering Receptor Expressed on Myeloid Cells 1 (TREM-1) showed substantial binding affinities with R. sativus phytochemicals, including quercetin, lutein, and violaxanthin, according to a molecular docking study. These interactions imply that R. sativus may lessen RA symptoms by suppressing immunological overactivation and lowering inflammation since TREM-1 is implicated in enhancing inflammatory responses. Furthermore, ADMET analysis shed light on the pharmacokinetics of the bioactive found in R. sativus. Certain substances, including β-carotene and Upadacitinib, exhibited good metabolic stability and bioavailability, whereas others had restricted absorption and possible safety hazards. This emphasizes the necessity of more in vivo research to confirm the drugs' efficacy and safety. Despite these encouraging results, it is important to recognize several limitations. Converting these findings into therapeutic applications is difficult due to the lack of thorough in vivo and clinical investigations.

2.7. Conclusion

The study reveals the benefits of using *R. sativus* in the management of RA. Its multi-targeted therapeutic potential is highlighted by the combination of molecular docking and network pharmacology. Further studies are needed to confirm these results through clinical and experimental trials, providing up the possibilities for the creation of innovative natural anti-rheumatic medications.

Author contributions

M.R.V. conceptualized, designed the study, writing the original draft. P.R. writing, review, data collection and supervision. P.B. methodology. M.Y. Data collection. S.P. writing, review and supervision. Subsequently, all authors critically reviewed and contributed to the manuscript’s refinement.

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Consent of Publication

Not Applicable

Ethical approval

Not applicable.

Clinical trial number

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Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

The data utilized in this study can be obtained from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used Grammarly, Inc. to check the grammar and Turnitin to check the plagiarism. AI was used for refining the language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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