Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 18s, 2025
https://www.theaspd.com/ijes.php

Molecular insights and Therapeutic prospects for the targeted treatment of Rheumatoid arthritis through in silico investigation of bioactive substances from Eranda (Ricinus communis Linn).

Dr. Soundarya R J[1], Dr. Sri Venkata Krishnan V[2], Dr. Shweta Yaragatti[3], Dr. Santhosh N[4*]

[1]Assistant Professor, Department of Dravyaguna, KAHER's Shri B.M.K Ayurveda Mahavidyalaya, Belagavi – 590003, Karnataka, India, soundaryagrj56@gmail.com
[2]Post graduate scholar, Department of Dravyaguna, KAHER's Shri B.M.K Ayurveda Mahavidyalaya, Belagavi – 590003, Karnataka, India, srivenkatakrishnan1999@gmail.com
[3]Assistant Professor, Department of Dravyaguna, KAHER's Shri B.M.K Ayurveda Mahavidyalaya, Belagavi – 590003, Karnataka, India, shwetay.kaher@kleayurworld.edu.in
[4]Post graduate scholar, Department of Dravyaguna, KAHER's Shri B.M.K Ayurveda Mahavidyalaya, Belagavi – 590003, Karnataka, India, santhoshgowdabelli79@gmail.com
Corresponding author: Dr. Santhosh N
For Correspondence Email: santhoshgowdabelli79@gmail.com

Abstract:

Numerous studies indicate that Eranda (Ricinus communis Linn) has anti-inflammatory, anti-diabetic, and anti-fertility properties in addition to its ability to scavenge free radicals. Eranda's favourable qualities make it an excellent choice to be used as a medication for rheumatoid arthritis. Molecular docking technology and network pharmacology were used, however, in order to have a thorough grasp of how the various active plant compounds present in Eranda combine to produce therapeutic effects on RA. Through data mining, 25 active Eranda phytoconstituents and 36 IHD-intersecting genes were identified, and they were then further investigated for network pharmacology study. Thus, we discovered three key chemicals (Quercetin, Ellagic acid, and Apigenin) and three key targets (EGFR, SRC, and PDGFRA). A common-target enrichment study was then performed. The Purine metabolism pathway, the VEGF Signalling pathway, and the EGFR tyrosine kinase inhibitor resistance system were the main pathways that were modified, according to the KEGG enrichment data. Three core chemicals from Eranda: Apigenin, Ellagic Acid, and Quercetin has demonstrated a strong affinity for core target active sites. EGFR, SRC, and PDGFRA, according to the molecular docking studies, which also exhibited good docking scores. This investigation revealed Eranda's pharmacological and molecular modes of action against rheumatoid arthritis. Additionally, the study provided a theoretical framework for further research on the pharmacological targets and processes of Eranda.

Keywords: *Eranda (Ricinus communis Linn), Network pharmacology, Molecular Insights, Rheumatoid Arthritis, Aamavata.*

INTRODUCTION:

Rheumatoid arthritis (RA) is a prevalent autoimmune condition which is typified by persistent swelling of the joint tissue. The development of RA is believed to be influenced by environmental factors, genetics, and infection. About 50% of the patients have wrist and interphalangeal joints that are swollen, painful, and deformed.

Some critical internal structures, including as the kidneys, heart, lungs, and digestive tract, may also be impacted in more severe cases, which may also exhibit joint deformity and functional restrictions.[1]

Rheumatoid arthritis affected an estimated 17.5 million persons worldwide in 2020, spanning all age groups. This is a 121% increase (117–125) since 1990. Since 1990, the age-standardized global prevalence rate has increased by 14·1% (12·7–15·4) to 208·8 instances (186·8–241·1) per 100,000 people. Rheumatoid arthritis was more frequent in women than in men across all estimating years. Rheumatoid arthritis is expected to affect 31.7 million people globally by 2050, with women accounting for 68.7% of those affected.[2] The incidence, prevalence, and DALY rates in India increased 2.76–3.38 times in 2021 compared to 1990.[3]

The adverse effects of Western anti-RA medications include suppression of immune system, gain in weight, diabetes mellitus, and bone quality deterioration. Increase in blood pressure, GI distress, liver damage, leukocytopenia, diffuse parenchymal lung disease, polyneuritis, infection of skin, and bone marrow mutilation.[4]

Aamavata [the imbalanced air (vata) carries the toxin (ama)] may be connected to RA, according to Ayurveda.[5] Bhavamishra describes Eranda (Ricinus communis Linn) Moola (Root) as Ama Maruta hara, (which eliminates the poisons carried by unbalanced air) and is intimately related to Aamavata (Rheumatoid arthritis).[6]

Eranda possesses antibacterial, antioxidant, hepatoprotective, ant filarial, and anti-asthmatic qualities. Furthermore, the roots of the plant are used in a variety of formulations for the treatment of rheumatic and neurological problems, including as sciatica, lumbago, and pleurodynia, as reported in Wealth of India. Additionally, the roots have anti-inflammatory, anti-diabetic, and anti-fertility actions in addition to scavenging free radicals.[7]

Through its ability to forecast the complex "drug-target-disease" interaction, network pharmacology provides a biological picture of illness and drug action mechanisms, which is useful for clinical drug safety and effectiveness evaluation.[8] In Additionally, the multi-component, multi-target, and regulatory network can disclose the drug's mechanism of action, which is especially appropriate for researching the mechanism of herbal compounds and their intricate constituents from a "holistic perspective."

Understanding the connection between (Ricinus communis Linn) (RC) molecular features and active drugs, against RA is made easier by the drug-target network. Thus, network pharmacology analysis of RC on RA targets is applied in this study.

MATERIALS AND METHODS:

Screening of active plant compounds of Eranda and associated illness targets:

The phytochemical contents of Eranda (Ricinus communis L) were ascertained by searching PubMed[9] research articles and databases such as IMPPAT[10] and Dr. Dukes[11]. Since they might not be the primary pharmacological targets, simple structured molecules and non-unique (Basic) compounds were then removed by eliminating duplicates. We then made many ADME element predictions using the SwissADME [12] database.

The collected phytochemicals were primarily tested for drug likeness and oral bioavailability. The target of Eranda's bioactive components was identified using Binding DB. [13] a similarity-based web service, with a similarity score of ≥0.85. Once we had the disease targets linked to the chemical, we standardized the target names using UniProtKB.[14]

Identifying overlapping targets and RA disease targets:

Utilizing the GeneCards[15] & HPA[16] database platforms, data on targeted therapies linked to RA was acquired. To find targets related to rheumatoid arthritis, the term "Rheumatoid arthritis" was employed. The intersecting targets from rheumatoid arthritis and Eranda were screened for using the Venny 2.1.0 software.

Establishing Networks of Interactions Between Proteins:

To gain information into the PPI network, an easy interface consisting of overlapping specific genes was constructed using STRING [17] version 11.0, depending on the drug-protein association for important bioactive compounds in Eranda. The preciseness of the research was attempted by calculating the protein's interaction with the species "Homo sapiens," using a seventy percent similarity (0.700) high-assurance level.

Analysis of KEGG Pathway Enrichment:

The PPI network and the top 10 KEGG pathways were then downloaded from the string database after intersecting targeted genes were added, Homo sapiens was selected as the species, and an FDR value of 0.5 was maintained.

Network building and topological analysis for Phytocompounds-Target-Pathways:

Cytoscape[18] Target genes, bioactive plant active components, and pathways were added, and the network was constructed using software version 2.7. We built the Phyto-Gene-Pathway network and analysed it. The Network Analyzer tool was utilized to conduct a topological investigation. The main phytochemicals in Eranda and the main treatment targets for RA were determined by degree.

Molecular Docking:

The RSCB PDB[19] and Pubchem databases provided the crystal structures of the top three target proteins and the top three compounds, respectively. To stabilize the protein structures, polar connections were created and water molecules were removed using the Biovia DS program. PyRx software[20] was used to automatically identify binding sites, and the docking approach was used to estimate the binding interaction of top target proteins and ligands. The Biovia Discovery Studio program has been used to illustrate the interaction with the best docking scores in two and three dimensions.

RESULTS:

Analysis of the phytochemicals in Ricinus communis with databases:

There was a total of 69 phytochemicals which were derived from two databases namely 1. IMPPAT and Dr. Dukes Phytochemical and Ethnobotanical Databases. Out of this we got 66 phytochemicals after sorting the duplicates. The SwissADME and PubChem databases were used to screen for toxicity and ADME before phytochemicals were chosen based on their oral absorption, bioavailability, and Lipinski violation. Using the BindingDB and Uniprot databases, we gathered and discovered 62 target genes in total related to these 25 active phytochemicals.

Segregation of over lapping targets:

'Rheumatoid arthritis' was the term used in the databases Gene cards and Human Protein Atlas (HPA) and a total of 6673 disease targets were found in both the disease after sorting them. These gene targets were intersected with the Phyto-targets so as to find overlapping targets using Venny 2.1. The targets of Ricinus communis (62) was made to intersect with 6673 targets of Rheumatoid arthritis. Finally, we found out 36 common targets among the both as overlapping targets which is shown in the fig.1.

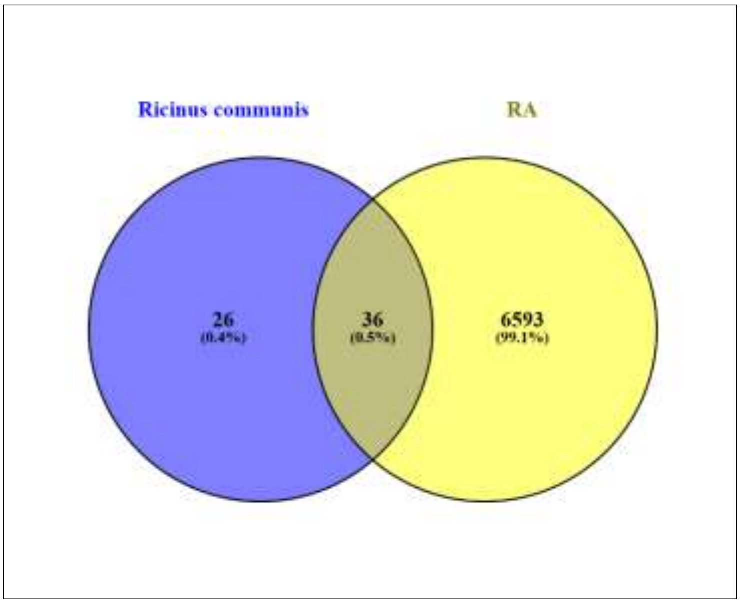

Fig. 1

PROTEIN-PROTEIN INTERACTION:

The network of Protein-protein interaction was made using the targets which were acquired from Venny 2.1. With selecting the criteria as "Homo sapiens" the overlapping targets 36 of Ricinus communis were uploaded and the results were derived with a medium degree of confidence 0.50. This is given in the fig.2.

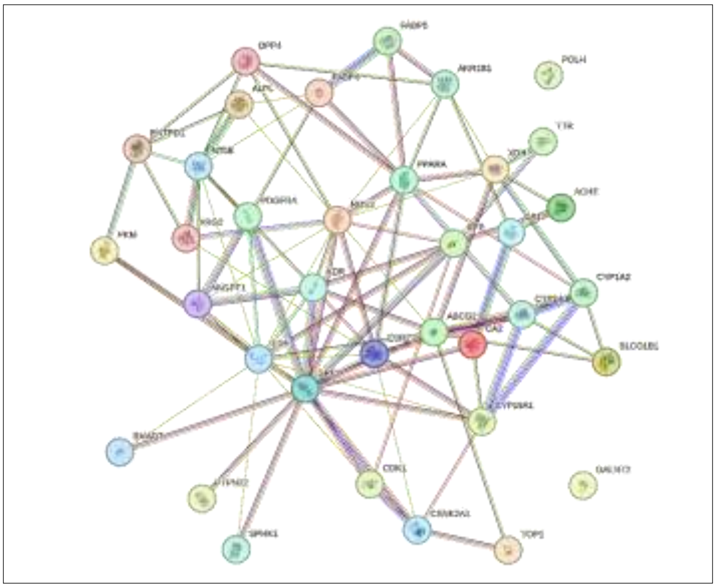

Fig. 2

KEGG PATHWAY ANALYSIS:

The signalling pathways were investigated by KEGG functional enrichment analysis using the STRING database. In order to determine how the root of Ricinus communis functions through this pathway in the chosen disease, a total of ten pathways related to Rheumatoid arthritis were gathered and examined. In Figure 3, these rheumatoid arthritis pathways are shown.

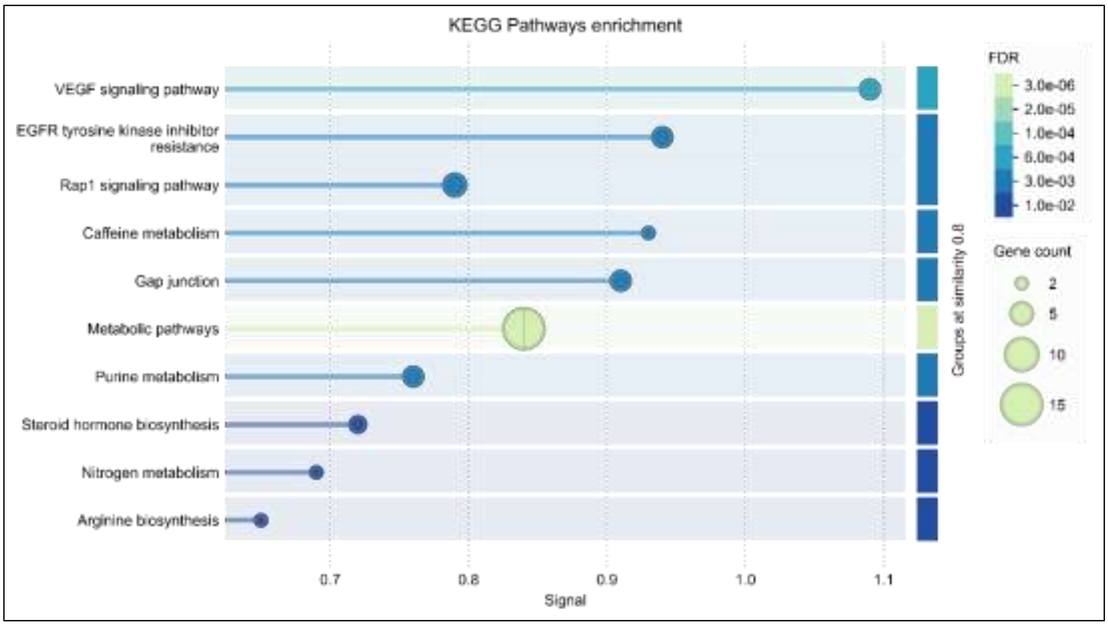

Fig. 3 Target – Phytochemicals – Pathway construction:

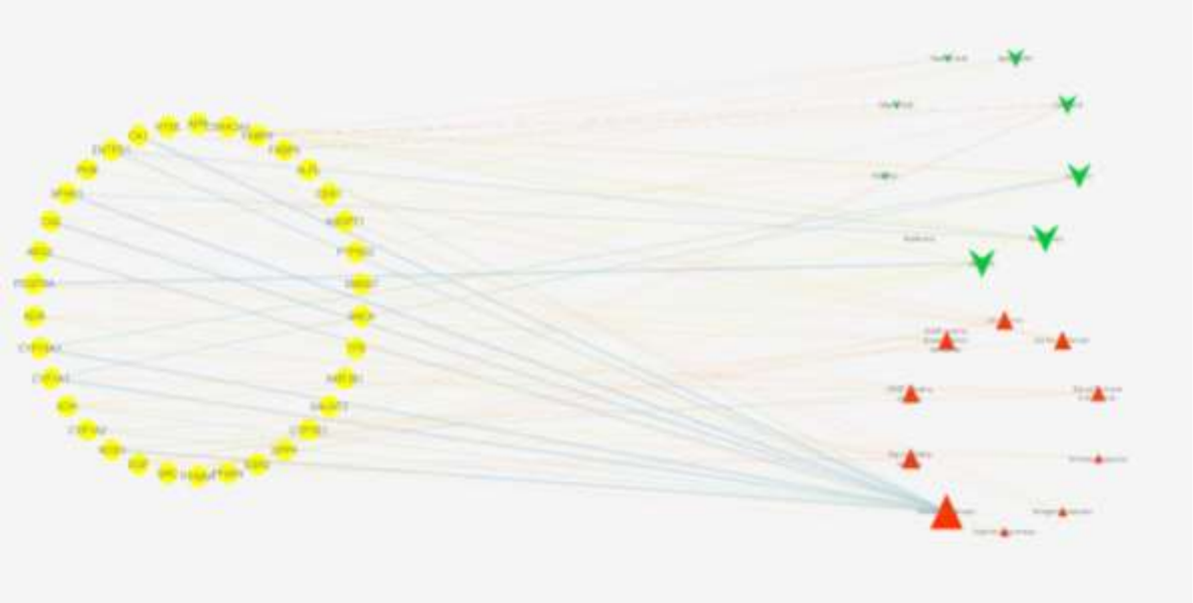

Fig.4 The interaction link between nine key active components, 34 overlapping targets, and ten significantly enriched KEGG pathways was constructed using Cytoscape 3.7.2 software (Fig.4).

MOLECULAR DOCKING:

Molecular docking was used to investigate possible binding processes and the validity of the networks between the three hub targets and the three bioactive phytochemicals. Three significant phytochemicals, Apigenin, Ellagic acid, and Quercetin, most likely showed a high interaction with the three primary targets identified based on binding energies ≥ 5. (Table 1)

Bio Actives	Binding Affinity		
	EGF (1nzi)	SRC (5ogj)	PDGFRA (6jol)
Apigenin	-6.4	-7.9	-9.8
Ellagic Acid	-6.3	-8.2	-7.4
Quercetin	-6.6	-7.7	-9.9

Table 1: Protein Docking of Ricinus communis in RA

DISCUSSION:

Eranda's molecular mechanism of action against RA was examined using two computational methods: Network pharmacology and molecular insights. Considering this, we discovered that Eranda included four essential compounds: Apigenin, Ellagic acid and Quercetin. Certain phytochemicals in Eranda have been discovered to have a specific effect on RA, according to recent studies.

Apigenin:

Research found that Apigenin decreased the collagenase activity linked to rheumatoid arthritis (RA) and dose-dependently suppressed the creation of nitric oxide (NO) in RAW 264.7 macrophage cells produced by lipopolysaccharide (LPS). Apigenin pretreatment also decreased the expression of cyclooxygenase-2 (COX-2) generated by LPS. Furthermore, apigenin significantly decreased the adherence of monocytes to the HUVEC monolayer caused by tumour necrosis factor-alpha (TNF-alpha).[21]

ELLAGIC ACID:

In the mouse model, EA therapy reduced the oedematous swelling of the foot and paw, synovitis, pannus development, and bone resorption, all of which are factors linked with AIA. EA's anti-arthritic impact was mediated by the overexpression of anti-inflammatory cytokines and the downregulation of pro-inflammatory ones. EA may therefore provide RA an extra therapeutic approach.[22] By downregulating the MTA1/HDAC1 complex and increasing HDAC1 deacetylation-mediated Nur77 expression, EA caused apoptosis in MH7A cells while suppressing growth, swelling, and cellular oxidative stress. Further in vivo studies showed that EA decreased the extent of RA in the CIA rat model.[23]

QUERCETIN:

In a rat model of RA, quercetin decreases the particular functioning of ADA in joint connective tissue, boosts body weight, decreases jaw volume, downregulates ADA gene activity, and decreases levels of RA cytokines like interleukin-1β, interleukin-6, and tumour necrosis factor-α, as well as rheumatoid factor, C-reactive protein, and anti-cyclic citrullinated peptide RA biomarker. These findings demonstrate that pure quercetin has a potential anti-inflammatory impact against RA disease via inhibiting the ADA enzyme.[24]

The creation of the chemical-gene route and the target-chemical network revealed that EGF, SRC, and PDGFRA were the primary targets. Since they are connected to the vital plant active constituents of Eranda, they may be primary targets for the therapy of RA.

EGF:

In RA patients' synovial tissues, AREG was the most abundant of the seven EGF-like growth factors. RA-FLS was encouraged to multiply and release a number of proinflammatory cytokines, including angiogenic factors, by recombinant human AREG. These findings imply that RA pathophysiology with synovial hyperplasia may be related to increased AREG expression in synovial tissues.[25]

SRC:

According to reports, synovial cells and synovial macrophages in RA patients express active Src. Furthermore, in rodents, it has been demonstrated that SFK and Src depletion improves arthritis. According to the study, rats with arthritis have higher levels of Src and Fyn mRNA expressions, while dasatinib, an SFK inhibitor, reduces arthritis symptoms and Src and Fyn expressions in the CIA model.[26]

PDGFRA:

Studies reveal a connection between RTK PDGFR activation and TGF-β for invadosome development in RA-FLS. TGF-β triggers the production of PDGF-B, which is controlled by the TβR1/Smad and PI3K pathways. These findings discovered PDGFR as an essential RTK required for the robust invadosome-forming phenotype of RA synovial cells and suggest that an overactive TGF-β/PDGFR pathway plays a role in cartilage breakdown processes.[27]

Therefore, we hypothesize that Eranda may have an anti-RA effect via altering these significant RA-related disease targets.

Additional investigation on the mechanism of action was conducted using KEGG Pathways. Eranda's pharmacological effects on RA were closely linked to the top ten KEGG pathways involved in signalling.

PURINE METABOLISM:

In mice and humans, L-arginine directly inhibited TNFα-induced osteoclastogenesis; in all three animals, it also reduced the loss of bone and inflammation of joints. L-arginine induced inflammatory osteoclasts by switch from glycolysis to oxidative phosphorylation, which increased ATP synthesis, purine metabolism, and inosine and hypoxanthine levels, according to RNA-seq and MS studies. Adenosine deaminase inhibitors, which prevent the formation of inosine and hypoxanthine, removed the suppression of L-arginine in osteoclastogenesis both in vitro and in vivo. Arginine levels are changed in individuals with RA and those without RA. [28]

Vascular Endothelial Growth Factor Signalling Pathway:

Both VEGF receptors (VEGFR) 1 and 2, Src, protein kinase C (PKC), and p38 MAPK were inhibited to reduce the VEGF-induced RANKL production. The suppression of VEGFR1 and 2, Src, PKC, and p38 MAPK reduced the osteoclast development from monocytes that VEGF promoted in the absence of RANKL. The monocytes transformed into osteoclasts during coculturing with VEGF-stimulated RA synovial fibroblasts, and suppression of Src and PKC pathways reduced osteoclastogenesis. In RA, VEGF has two effects on osteoclastogenesis: it directly induces osteoclastogenesis from precursors and stimulates the synthesis of RANKL in synovial fibroblasts through the Src and PKC pathways. For RA-related bone loss, the VEGF-RANKL axis may be a promising therapeutic target.[29]

EGFR tyrosine kinase inhibitor resistance Pathway:

A study found that erlotinib, a blocker of the tyrosine kinase epidermal growth factor receptor (EGFR), reduces the extent of developed collagen-induced arthritis in mice, a model of RA, by targeting synovial fibroblasts, endothelial cells, and osteoclasts. In vitro, erlotinib suppressed the growth of human endothelial cells and the production of mouse osteoclasts, and it was linked to a decrease in blood vessels and osteoclasts in autoimmune arthritis. In vitro, erlotinib also prevented human synovial fibroblasts from proliferating and producing cytokines. Furthermore, the synovium of RA patients and mice with collagen-caused arthritis showed elevated expression also activated EGFR. These findings suggest that EGFR plays a significant role for pathogenesis of RA and that EGFR suppression could aid in the treatment of the condition altogether.[30]

Additionally, a strong docking relationship between the three essential targets and the three previously identified core components was verified using molecular docking. Quercetin interacts with PDGFRA to provide the lowest binding energy of all of the examined compounds, measuring -9.9 kcal/mol by this we can conclude that Quercetin have good interaction and Higher binding affinity towards PDGFRA.

According to this study, Eranda may potentially help cure RA patients by intricately regulating multiple pathways. This study looked into Eranda's primary components, possible targets of the disease, and methods of action in RA. Some proteins and compounds might not have been incorporated into the study because to database limitations, and effectiveness and safety assessments are still required & are obtained by pre-clinical and clinical trials.

CONCLUSION:

We can conclude that, by acting on important targets like EGF, SRC, and PDGFRA through the possible components apigenin, ellagic acid, and quercetin, Eranda may aid in modulating the Purine metabolism pathway, VEGF Signalling pathway, and EGFR tyrosine kinase inhibitor resistance system. Our study found that three key Eranda compounds—Apigenin, Ellagic acid, and Quercetin— demonstrated excellent connection and high docking scores with the functional sites of the main targets PDGFRA, SRC, and EGF. More pre-clinical and clinical studies on such compounds will be required to develop an effective therapeutic entity for the treatment of RA.

Eranda has an active ingredient called quercetin, which has a remarkable affinity for binding to three important protein targets in the RA pathway. This may help explain the pathophysiology of RA and make it a novel bioactive phytochemical. This proves Eranda's suitability as a RA therapy. The in-silico approach offers a reliable way to identify potential therapeutic targets for drugs, which can guide the design of wet lab studies for experimental validation and aid in the development of multi-compound RA treatment plans.

ACKNOWLEDGMENT:

Nil

CONFLICT OF INTEREST:

There is no conflict of interest.

ABBREVIATIONS:

RC – (Ricinus communis Linn)
RA – Rheumatoid Arthritis
DALY – Disability adjusted life years
GI – Gastro Intestinal
IMMPAT - Indian Medicinal Plants, Phytochemistry and Therapeutics
ADME - Absorption, distribution, metabolism, and excretion
HPA – Human Protein Atlas
PPI – Protein Protein Interaction
KEGG - Kyoto Encyclopaedia of Genes and Genomes

PDB – Protein Data Bank
PYRX - Python Prescription
EGF – Epidermal Growth Factor
SRC - SRC proto-oncogene, non-receptor tyrosine kinase (Sarcoma)
PDGFRA - Platelet-derived growth factor receptor alpha
VEGF - Vascular Endothelial Growth Factor A
EGFR – Epidermal growth factor receptor

REFERENCES:

1. Cai Y, Zhang J, Liang J, Xiao M, Zhang G, Jing Z, Lv L, Nan K, Dang X. The Burden of Rheumatoid Arthritis: Findings from the 2019 Global Burden of Diseases Study and Forecasts for 2030 by Bayesian Age-Period-Cohort Analysis. J Clin Med. 2023 Feb 6;12(4):1291. doi: 10.3390/jcm12041291. PMID: 36835827; PMCID: PMC9959633.
2. GBD 2021 Rheumatoid Arthritis Collaborators. Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology [Internet]. 2023 Oct 1;5(10):e594–610. Available from: https://pubmed.ncbi.nlm.nih.gov/37795020/#:~:text=Findings%3A%20In%202020%2C%20an%20estimated
3. Shi W, Liang X, Zhang H, Li H. Burden of rheumatoid arthritis in India from 1990 to 2021: insights from the Global Burden of Disease Database. Frontiers in Medicine. 2025 Feb 14;12.
4. Bullock J, Rizvi SAA, Saleh AM, Ahmed SS, Do DP, Ansari RA, Ahmed J. Rheumatoid Arthritis: A Brief Overview of the Treatment. Med Princ Pract. 2018;27(6):501-507. doi: 10.1159/000493390. Epub 2018 Sep 2. PMID: 30173215; PMCID: PMC6422329.
5. Srikanta Murthy KR. Madhava Nidana of Madhavakara. English translation. 2013:95.
6. Editor Dr. G.S.Pandey, commentary by Prof. KrushnachandraChunekar, Bhavaprakasha Nighantu, Guduchyadi varga, Verse – 55, Choukamba publications, 2020 Edition.
7. Mosleh Mohammad Abomughaid, John Oluwafemi Teibo, Opeyemi Abigail Akinfe, Abiodun Mohammed Adewolu, Titilade Kehinde Ayandeyi Teibo, Afifi M, et al. A phytochemical and pharmacological review of Ricinus communis L. Deleted Journal. 2024 Jun 8;6(6).
8. Chandran U, Mehendale N, Patil S, Chaguturu R, Patwardhan B. Network pharmacology. In: Innovative Approaches in Drug Discovery. 2017. p. 127–64.
9. PubMed, National Center for Biotechnology Information (NCBI), at the U.S. National Library of Medicine (NLM). 1996, PubMed Home page Available from: https://pubmed.ncbi.nlm.nih.gov/.
10. Karthikeyan M, Bagavathy SK, Vivek-Ananth RP, Bharath Chand RP, Aparna SR, Mangalapandi P, et al. IMPPAT: A curated database of Indian medicinal plants, phytochemistry and therapeutics. Sci Rep 2018;8:4329.
11. Dr. Duke's Phytochemical and Ethnobotanical Databases. U.S. Department of Agriculture, Agricultural Research Service. 1992-2016. Available from: http://phytochem.nal.usda.gov/. [Last accessed on 20th Aug 2022]. doi: 10.15482/USDA.ADC/1239279
12. Daina A, Michielin O, Zoete V. SwissADME. A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 2017;7:42717.
13. Liu T., Lin Y., Wen X., Jorissen R.N. and Gilson M.K.: BindingDB: a web-accessible database of experimentally determined protein-ligand binding affinities., Nucleic Acids Res., 2007, 35(Database issue), D198–201.
14. Bairoch A., Apweiler R., Wu C.H., Barker W.C., Boeckmann B., Ferro S., Gasteiger E., Huang H., Lopez R., Magrane M., Martin M.J., Natale D.A., O'Donovan C., Redaschi N. and Yeh L.L.: The Universal Protein Resource (UniProt), **Nucleic Acids Res.**, 2005, 33(Database issue), D154-D159.
15. Stelzer G., Rosen N., Plaschkes I., Zimmerman S., Twik M., Fishilevich S., Stein T.I., Nudel R., Lieder I., Mazor Y., Kaplan S., Dahary D., Warshawsky D., Guan-Golan Y., Kohn A., Rappaport N., Safran M. and Lancet D.: The GeneCards suite: From gene data mining to disease genome sequence analyses, **Curr Protoc Bioinformatics.**, 2016, 54(1), 1.30.1-1.30.33.
16. The Human Protein Atlas. Human Protein Atlas [Internet]. Proteinatlas.org. 2019. Available from: https://www.proteinatlas.org/
17. Szklarczyk D., Kirsch R., Koutrouli M., Nastou K., Mehryary F., Hachilif R., Gable A.L., Fang T., Doncheva N.T., Pyysalo S., Bork P., Jensen L.J. and Mering C.V.: The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest, **Nucleic Acids Res.**, 2023, 51(D1), D638–646
18. Shannon P., Markiel A., Ozier O., Baliga N. S., Wang J. T., Ramage D., Amin N., Schwikowski B. and Ideker T.: Cytoscape: A software environment for integrated models of biomolecular interaction networks, **Genome Res.**, 2003, 13(11), 2498–2504.

19. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE.. The Protein Data Bank. Nucleic Acids Res. January, 2000; 28(1); 235-242.
20. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol. 2015;1263; 243–250.
21. Lee JH, Zhou HY, Cho SY, Kim YS, Lee YS, Jeong CS. Anti-inflammatory mechanisms of apigenin: inhibition of cyclooxygenase-2 expression, adhesion of monocytes to human umbilical vein endothelial cells, and expression of cellular adhesion molecules. Arch Pharm Res. 2007 Oct;30(10):1318-27. doi: 10.1007/BF02980273. PMID: 18038911.
22. Allam G, Mahdi EA, Alzahrani AM, Abuelsaad AS. Ellagic acid alleviates adjuvant induced arthritis by modulation of pro- and anti-inflammatory cytokines. Cent Eur J Immunol. 2016;41(4):339-349. doi: 10.5114/ceji.2016.65132. Epub 2017 Jan 24. PMID: 28450796; PMCID: PMC5382880.
23. Song H, Wu H, Dong J, Huang S, Ye J, Liu R. Ellagic Acid Alleviates Rheumatoid Arthritis in Rats through Inhibiting MTA1/HDAC1-Mediated Nur77 Deacetylation. Mediators Inflamm. 2021 Dec 9;2021:6359652. doi: 10.1155/2021/6359652. PMID: 34924813; PMCID: PMC8677414.
24. El-Said KS, Atta A, Mobasher MA, Germoush MO, Mohamed TM, Salem MM. Quercetin mitigates rheumatoid arthritis by inhibiting adenosine deaminase in rats. Mol Med. 2022 Feb 22;28(1):24. doi: 10.1186/s10020-022-00432-5. PMID: 35193490; PMCID: PMC8862293.
25. Yamane S, Ishida S, Hanamoto Y, Kumagai K, Masuda R, Tanaka K, Shiobara N, Yamane N, Mori T, Juji T, Fukui N, Itoh T, Ochi T, Suzuki R. Proinflammatory role of amphiregulin, an epidermal growth factor family member whose expression is augmented in rheumatoid arthritis patients. J Inflamm (Lond). 2008 Apr 27;5:5. doi: 10.1186/1476-9255-5-5. PMID: 18439312; PMCID: PMC2396620.
26. Yalçın Kehribar D, Özgen M, Yolbaş S, Yıldırım A, Önalan Etem E, Çiftçi O, Özercan İH, Koca SS. The inhibition of Src kinase suppresses the production of matrix metalloproteinases in from synovial fibroblasts and inhibits MAPK and STATs pathways. Turk J Med Sci. 2021 Aug 30;51(4):2142-2149. doi: 10.3906/sag-2008-274. PMID: 33714238; PMCID: PMC8569788.
27. Charbonneau M, Lavoie RR, Lauzier A, Harper K, McDonald PP, Dubois CM. Platelet-Derived Growth Factor Receptor Activation Promotes the Prodestructive Invadosome-Forming Phenotype of Synoviocytes from Patients with Rheumatoid Arthritis. The Journal of Immunology [Internet]. 2016 Apr [cited 2025 May 25];196(8):3264–75. Available from: https://journals.aai.org/jimmunol/article/196/8/3264/105647/Platelet-Derived-Growth-Factor-Receptor-Activation
28. Cao S, Li Y, Song R, Meng X, Fuchs M, Liang C, Kachler K, Meng X, Wen J, Schlötzer-Schrehardt U, Taudte V, Gessner A, Kunz M, Schleicher U, Zaiss MM, Kastbom A, Chen X, Schett G, Bozec A. L-arginine metabolism inhibits arthritis and inflammatory bone loss. Ann Rheum Dis. 2024 Jan 2;83(1):72-87. doi: 10.1136/ard-2022-223626. PMID: 37775153; PMCID: PMC10803985.
29. Kim HR, Kim KW, Kim BM, Cho ML, Lee SH. The effect of vascular endothelial growth factor on osteoclastogenesis in rheumatoid arthritis. PLoS One. 2015 Apr 20;10(4):e0124909. doi: 10.1371/journal.pone.0124909. PMID: 25894998; PMCID: PMC4404365.