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# Exploring the role of curcumin induced STAT3 inhibition in Rheumatoid Arthritis treatment

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***Abstract***— Rheumatoid Arthritis (RA) is a chronic autoimmune disease that mostly affects the joints, and causes the weakening of tendons and ligaments. The common symptoms of RA include tender joints, fever, fatigue, and often
rheumatoid nodules under the skin. STAT3 is a transcription factor protein that regulates the expression of pro-inflammatory cytokines. Persistent activation of the JAK-STAT pathway is due to the dysregulation of cytokine signalling contributing to synovial inflammation. Therefore, STAT3 inhibitors are required to treat the underlying disease rather than only curing symptoms. The primary active compounds found in Curcuma longa consist of 3 curcuminoids- curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Curcumin is the active ingredient that has shown anti-inflammatory effects through modulation of the JAK-STAT pathway. By promoting the dephosphorylation of STAT 3, curcumin efficiently inhibits its activation and downstream signalling. So, for this we use a ligand i.e. curcumin which inhibits the activity of STAT 3 protein, thus reducing the symptoms of RA. We are essentially assessing the interaction between the ligand and the protein while working on molecular docking. In-silico, assays demonstrated that curcumin reduced arthritis scores and enhanced inflammatory infiltration. Docking studies can show the binding affinity between ligands and proteins, thus providing predictions on the strength of their potential interaction. So, using molecular docking we infer that curcumin has lower binding free energy than other well-known STAT 3 inhibitors and can target RA symptoms. ***Keywords***— Rheumatoid Arthritis, Curcumin, STAT 3 ,JAK-STAT pathway, Molecular Docking

## 1. INTRODUCTION:

Rheumatoid arthritis (RA) can be explained as a systemic autoimmune condition characterized by ongoing inflammation. This Inflammation can result in adverse effects on joints as well as other organs, such as the heart, kidneys, lungs, digestive system, eyes, skin, and nervous system. After examination of several types of arthritis, they have been classified as non-inflammatory arthritis such as osteoarthritis, and inflammatory arthritis which can be caused by several factors such as crystal deposition (pseudo gout, basic calcium phosphate disease, and gout), as well as those triggered by bacterial and viral infections (Staphylococcus aureus, Neisseria gonorrhoea, complications of Lyme disease, Parvovirus, Enterovirus) or by autoimmune mechanism. [1]

RA affects about 0.4%-1.3% of the population, with variation in prevalence based upon factors like gender (affecting women 2-3 times more than men), age (highest frequency of new RA diagnoses occurs in the 6th decade of life) along with demographics of the population under study (RA frequency rises from south to north and is most prevalent in urban areas as compared to rural areas). Therefore, RA stands out as one of the most common chronic inflammation conditions acquired. Clinical symptoms of RA have significant variations between the early stages of RA and inadequately treated later stages of the disease. Character general symptoms of early-stage RA include fatigue, flu-like sensations, swollen and tender joints, and morning stiffness, often accompanied by elevated C-reactive protein (CRP) along with an increased erythrocyte sedimentation rate (ESR). On the other hand, insufficiently treated RA presents a much more complex clinical picture which includes the emergence of serious systemic manifestations including pleural effusions, lung nodules, interstitial lung disease, along with lymphomas, vasculitis in small or medium-sized arteries, keratoconjunctivitis, atherosclerosis, hematologic abnormalities (such as anaemia, leukopenia, neutropenia, eosinophilia, thrombocytopenia, or thrombocytosis), joint malalignment, loss of range of motion, bone erosion, cartilage destruction, and rheumatic nodules. It can be said that these systemic manifestations mainly arise due to the chronic inflammatory state in RA patients and also contribute to the heightened mortality rates.[2]

In RA synovial joints (typical single membrane synovium) undergo hyperplasia. This alteration is caused by increased migration and adhesion of activated immune and non-immune cells, guided by elevated concentrations of different chemokines and adhesion proteins. Additionally, significantly high levels of pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF-α), interleukins (IL) -1ß, -6, -7, -8, -12/IL-23, -15, -17, -18, -32, and interferon-γ (IFN-γ), which are produced by various cells in RA, along with growth factors like fibroblast growth factor— 2(FGF-2) and vascular endothelial growth factor, Which are primarily synthesized by synovial-like fibroblasts and macrophages and play crucial roles in clinical progression of RA, Thus leading to primary events of articular cartilage destruction and subchondral bone erosion, which ultimately leads to synovial joint failure.[3]

Various cytokines further activate the Jak (Janus-activated Kinase)-STAT (Signal Transduction and Activator of Transcription) pathway which serves as an intracellular signalling route. The JAK-STAT is a crucial signalling pathway for cytokine signalling which plays important roles in cell differentiation, apoptosis, regulating inflammation and immune function, etc.[4] Numerous studies showed abnormal activation of JAK-STAT during RA.[5] This indicates its involvement in pathological conditions of RA. Its activation induces the synthesis of both pro-inflammatory and anti-inflammatory cytokines, along with some locally destructive enzymes. These pro-and anti-inflammatory cytokines play a role in the pathogenesis of RA, including mediation of RA-associated pain e.g. cytokines TNF-α, IL-1, and IL-6 play a role in RA-associated pain through autoimmunity promotion, chronic inflammatory synovitis, and adjacent joint tissue destruction.[4]

In the Jak family, 4 protein tyrosine kinases are present i.e. Jak1, Jak2, Jak3, and tyrosine kinase (TYK2). These members are of different molecular weights and are highly conserved in the evolutionary process. These kinases function as dimers, either homo- or heterodimers, under phosphorylated conditions which are triggered by specific cytokine binding to their membrane-bound receptors. After phosphorylation, Jak dimers further recruit several additional signalling peptides, majorly from the STAT family. The STAT family is comprised of seven transcription factors: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 which are cytoplasmic proteins playing important roles in transcriptional activation as well as signal transduction. These contain six highly conserved functional domains, the N-terminal conserved domain, the helix domain, the DNA binding domain, the ligation domain, the SH2 domain, and the C-terminal transcriptional activation domain, out of which the SH2 domain allows for

specific recognition and docking of phosphorylated tyrosine's on cytokines receptor, JAK, and other STAT molecules.[5] Once dimerization takes place, either homo-or heterodimers, STAT peptides translocate across the nuclear membrane which ultimately initiates transcription with the assistance of coactivators. This transcriptional activation caused by STATs upregulates cytokines and other involved components of immune pathways expression, this establishes a positive feedback loop.[4]

STAT3 serves as the primary downstream regulator of the gp130 receptor and can be activated by various cytokines such as IL-6, IL-10, IFN-α/β, etc. Activation of STAT-3 majorly contributes to the progression of chronic arthritis, regulates the aberrant growth and survival traits of synovial cells in RA, and aggravates the clinical symptoms even further.

The pathogenic involvement of STAT3 in RA is supported by a no. of evidence from different sources, including:

1. Wang et al. and colleagues first observed that STAT3 showed DNA-binding activity in synovial mononuclear cells from patients with inflammatory arthritis.
2. Lee et al. discovered that STAT3 can inhibit FLS apoptosis, and can increase the activity of T cells along with promoted production of antibodies, thus indicating that STAT3 is involved in multiple links of RA pathogenesis.
3. Oike et al. observed that in collagen-induced arthritis model mice, p-STAT3 was highly expressed in the synovium and the cartilage, along with a significant reduction in inflammatory cytokines IL-17 and Il-6 in serum after STAT3 inhibition.[5]

Thus, it can be said that STAT3 plays a notable role in determining RA helper cell differentiation. Transfection of STAT3 siRNA inhibits CD4+ T cell differentiation into Th17 cells and increases the proportion of Treg cells. From these results, it can be concluded that STAT3 is closely associated with articular inflammation and lymphocyte differentiation, and STAT3 might be a new target for the treatment of RA.[5]

Turmeric, scientifically known as *Curcuma longa*, is a fragrant herbaceous plant indigenous to Southeast Asia and is classified within the ginger family; India is the largest producer, consumer, and exporter of turmeric globally. Bright orange powder from turmeric rhizome has been an integral part of Ayurvedic cuisine and holistic medicine as a therapeutic herb for a very long time. Curcumin is identified as the most bioactive compound in turmeric and exerts antioxidant, anti-inflammatory, anti-angiogenic, and anti-tumor pharmacological effects without significant side effects. Multiple clinical trials are ongoing, mainly in oncology, obesity-related metabolic diseases, and neurology to investigate curcumin's health benefits. Multiple studies have also shown that curcumin and curcuminoids in turmeric could provide good protection against many chronic diseases by inhibiting inflammatory responses, lowering blood lipids, and improving blood sugar. Promising results have been shown in the effect of curcumin on Crohn's disease, colorectal and prostate cancer, ulcerative colitis, and autoimmune diseases such as rheumatoid arthritis and inflammatory bowel diseases. Therefore, it can be said that curcumin is not only effective in autoimmune disorders but is effective as an anti-inflammatory and anti-cancer agent.[6]

Currently, treatment regimens for RA consist of combinations of pharmaceuticals, weight-bearing exercises, and surgery. Weak opioids, NSAIDS, and corticosteroids are effective in managing pain and inflammation for a short period in low doses but their side effects outweigh the benefits.[7] The adverse effects of cDMARDs and the high cost of bDMARDs are limiting factors for accessing DMARD treatment. Surgery frequently raises the risk of infection and may cause dysregulation.[8] Natural remedies do not have such side effects and therefore can be used as treatment methods, Curcumin being a prospective natural medicine for RA. This study focuses on the use of curcumin as a ligand for the STAT 3 protein acting as an inhibitor resulting in a reduction of RA symptoms and reducing the onset.

STA21 is the control ligand taken for the study which is a proven STAT3 inhibitor. The activity of curcumin is compared against it to check for the efficacy of our compound of interest. From past literature, it can be observed that various studies have been performed to check the binding energy of numerous compounds with STAT3 to find efficient ligands and inhibitors, but limited studies are available on curcumin. In this paper, with the help of in silico studies, we will target STAT3 with curcumin to find out more efficient ways of treating Rheumatoid Arthritis.

## 2. METHODOLOGY

### *A. Data collection*

The compilation of selected natural compounds was derived from scientific literature, showcasing potential for suppressing the progression of rheumatoid arthritis. The PubChem database was used to get all the desired SMILE structures.

### *B. Preparation of target and ligand*

The PDB molecule 6NJS has A chain and sequence length of 562aa. The protein STAT3 (target) was produced from Pymol[9] for docking of the target protein with the selected compounds. All the polar hydrogen atoms were introduced and water molecules were taken out. The final structure of protein was then stored in PDB format. By using the software Open Babel, ligand (compound) SDF structures were transformed to MOL2 format and then stored.

### *C. Molecular docking using Swiss dock*

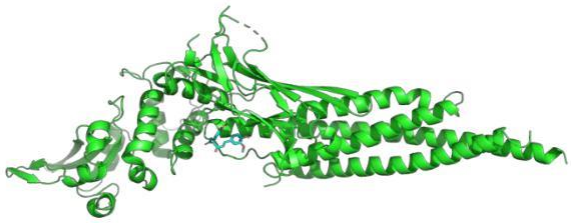
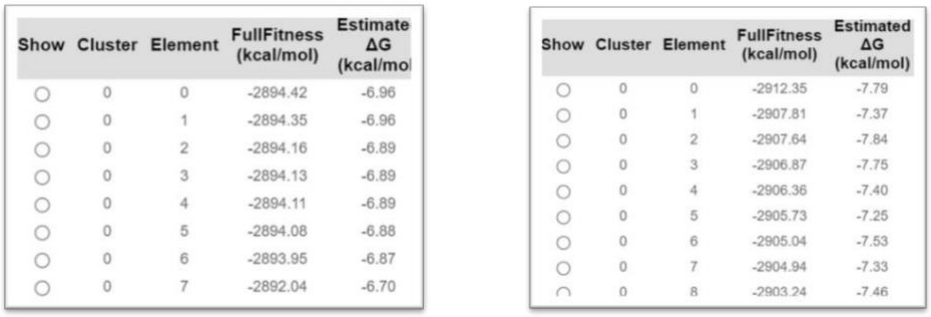


Fig.1. Docking interaction of Curcumin with STAT3

Molecular docking, a prominent in silico method for drug discovery, is widely used to predict the interaction between target proteins and various small molecules like drugs, inhibitors and ligands as shown in “Fig. 1,”. [9]Swiss dock is a web server which is designed for conducting protein-ligand docking simulations. Built upon the EADock DSS docking program, Swiss dock features a streamlined and integrated interface. Users can upload protein and ligand structures files, and the results are delivered via email. The docking scores determine the compounds, and ligands with binding energies lower than those of known inhibitors are considered for further analysis.[10]

## 3. RESULT:

The compound Curcumin satisfied the criteria with a binding energy of -7.84 kcal/mol which is lower than STA21, a recognized inhibitor of STAT3.The compound proved to be a more effective inhibitor than anticipated and the STA21 has a binding energy of -6.89 kcal/mol as shown below in “Fig. 2”.



| Show | Cluster | Element | FullFitness (kcal/mol) | Estimate ΔG (kcal/mo |
|---|---|---|---|---|
| ○ | 0 | 0 | -2894.42 | -6.96 |
| ○ | 0 | 1 | -2894.35 | -6.96 |
| ○ | 0 | 2 | -2894.16 | -6.89 |
| ○ | 0 | 3 | -2894.13 | -6.89 |
| ○ | 0 | 4 | -2894.11 | -6.89 |
| ○ | 0 | 5 | -2894.08 | -6.88 |
| ○ | 0 | 6 | -2893.95 | -6.87 |
| ○ | 0 | 7 | -2892.04 | -6.70 |

| Show | Cluster | Element | FullFitness (kcal/mol) | Estimated ΔG (kcal/mol) |
|---|---|---|---|---|
| ○ | 0 | 0 | -2912.35 | -7.79 |
| ○ | 0 | 1 | -2907.81 | -7.37 |
| ○ | 0 | 2 | -2907.64 | -7.84 |
| ○ | 0 | 3 | -2906.87 | -7.75 |
| ○ | 0 | 4 | -2906.36 | -7.40 |
| ○ | 0 | 5 | -2905.73 | -7.25 |
| ○ | 0 | 6 | -2905.04 | -7.53 |
| ○ | 0 | 7 | -2904.94 | -7.33 |
| ○ | 0 | 8 | -2903.24 | -7.46 |

Fig. 2. Estimated binding energies of STA21(control) and curcumin are shown here

## 4. LITERATURE SURVEY

Conduction of an in-depth literature search was performed using databases like PubMed and Google Scholar. The binding energy of various components tested as STAT 3 inhibitors for prevention of RA onset using molecular docking of inhibitors with STAT3 as given below in [Table 1].[11], [12], [13]

TABLE I
LIST OF STAT3 INHIBITORS

| **Inhibitor** | **ΔG (Kcal/mol)** |
|---|---|
| Flll32 | -6.69 |
| Stattic | -6.45 |
| Zoledronic Acid | -6.3 |
| Berberine | -6.15 |

The above-mentioned compounds when tested through docking showed positive results for treatment from plant-derived products such as berberine to drugs such as Flll32 which is a known drug for the treatment of Rheumatoid arthritis but as compared to all the above compounds Curcumin has a binding energy of -7.79 kcal/mol representing that it is potentially a better inhibitor of the protein and can serve as a more effective treatment for RA.[12], [14] Recent research suggests that curcumin have potential to overcome drug resistance, inhibit the metastatic potential of cancer cells. Recent studies also demonstrated curcumin’s ability to inhibit inflammatory genes such as TNF-α, COX-2, NF-κB, IL-6, and IL-1β, IL-8, IL-10, COX-1 and MMPs.[5], [14]

## 5. DISCUSSIONS

Due to the increasing prevalence of RA in silico strategies like molecular docking to develop drugs have become demand. A no. of studies have been conducted recently to check various compounds' ability as potential STAT 3 inhibitors by binding using docking including compounds like zoledronic acid, berberine, stattic, etc. with promising results.[12], [15]

Therefore, using molecular docking we are targeting STAT 3 using curcumin to find its efficacy. Compared to inhibitors like STA21, with a binding energy of -6.69 kcal/mol, curcumin has shown much promising results with a binding energy of -7.79 kcal/mol. Due to less binding energy of curcumin with STAT3, better inhibition would be there, thus preventing RA symptoms.[11]

## 6. Conclusion

As compared to other STAT3 inhibitors, curcumin with much lower binding energy has been proven as a potent inhibitor. However, more thorough research and studies would be required for the validation of the suggested model.

## 7. Future Aspect

The compound curcumin has shown promising results being a better ligand than other known compounds. The activity of the STAT3 pathway inhibited by curcumin is followed by suppression of the proliferative capacity of lung cancer cells. Further study and research can lead to more efficient treatment of rheumatoid arthritis, leveraging the advantages of plant-based remedies which potentially offer fewer side effects compared to conventional medications.[16]

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## 9. References

[1] A.-F. Radu and S. G. Bungau, “Management of Rheumatoid Arthritis: An Overview,” *Cells*, vol. 10, no. 11, p. 2857, Oct. 2021, doi: 10.3390/cells10112857.

[2] Y.-J. Lin, M. Anzaghe, and S. Schülke, “Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis,” *Cells*, vol. 9, no. 4, p. 880, Apr. 2020, doi: 10.3390/cells9040880.

[3] C. J. Malemud, “The role of the JAK/STAT signal pathway in rheumatoid arthritis,” *Ther. Adv. Musculoskelet. Dis.*, vol. 10, no. 5–6, pp. 117–127, Jun. 2018, doi: 10.1177/1759720X18776224.

[4] L. S. Simon *et al.*, “The Jak/STAT pathway: A focus on pain in rheumatoid arthritis,” *Semin. Arthritis Rheum.*, vol. 51, no. 1, pp. 278–284, Feb. 2021, doi: 10.1016/j.semarthrit.2020.10.008.

[5] Q. Ding *et al.*, “Signaling pathways in rheumatoid arthritis: implications for targeted therapy,” *Signal Transduct. Target. Ther.*, vol. 8, no. 1, p. 68, Feb. 2023, doi: 10.1038/s41392-023-01331-9.

[6] S. Tomaras, G. Keyßer, and E. Feist, “Curcumin: Useful add-on for Rheumatic Diseases?,” *J. Clin. Med.*, vol. 11, no. 10, p. 2908, May 2022, doi: 10.3390/jcm11102908.

[7] T. D. Mahajan and T. R. Mikuls, “Recent advances in the treatment of rheumatoid arthritis,” *Curr. Opin. Rheumatol.*, vol. 30, no. 3, pp. 231–237, May 2018, doi: 10.1097/BOR.0000000000000496.

[8] J. Bullock *et al.*, “Rheumatoid Arthritis: A Brief Overview of the Treatment,” *Med. Princ. Pract.*, vol. 27, no. 6, pp. 501–507, 2018, doi: 10.1159/000493390.

[9] S. Yuan, H. C. S. Chan, and Z. Hu, “Using PyMOL as a platform for computational drug design,” *WIREs Comput. Mol. Sci.*, vol. 7, no. 2, p. e1298, Mar. 2017, doi: 10.1002/wcms.1298.

[10] A. Grosdidier, V. Zoete, and O. Michielin, “SwissDock, a protein-small molecule docking web service based on EADock DSS,” *Nucleic Acids Res.*, vol. 39, no. suppl, pp. W270–W277, Jul. 2011, doi: 10.1093/nar/gkr366.

[11] Computational Biology Laboratory, Department of Biotechnology, Indian Institute of Technology Guwahati, Guwahati-781039, Assam, India, Biotech Hub, Centre for the Environment, Indian Institute of Technology Guwahati, Guwahati-781039, Assam, India, A. Kumar, and U. Bora, “Molecular docking studies on inhibition of Stat3 dimerization by curcumin natural derivatives and its conjugates with amino acids,” *Bioinformation*, vol. 8, no. 20, pp. 988–993, Oct. 2012, doi: 10.6026/97320630008988.

[12] J. Cao, L. Li, L. Xiong, C. Wang, Y. Chen, and X. Zhang, “Research on the mechanism of berberine in the treatment of COVID-19 pneumonia pulmonary fibrosis using network pharmacology and molecular docking,” *Phytomedicine Plus*, vol. 2, no. 2, p. 100252, May 2022, doi: 10.1016/j.phyplu.2022.100252.

[13] V. Janakiraman *et al.*, “Rheumatoid arthritis treatment with zoledronic acid, a potential inhibitor of GWAS-derived pharmacogenetics STAT3 and IL2 targets,” *Gene*, vol. 866, p. 147338, May 2023, doi: 10.1016/j.gene.2023.147338.

[14] J. J. Bright, “CURCUMIN AND AUTOIMMUNE DISEASE,” in *The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease*, vol. 595, B. B. Aggarwal, Y.-J. Surh, and S. Shishodia, Eds., in ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, vol. 595. , Boston, MA: Springer US, 2007, pp. 425–451. doi: 10.1007/978-0-387-46401-5_19.

[15] X. Liu *et al.*, “Natural medicines of targeted rheumatoid arthritis and its action mechanism,” *Front. Immunol.*, vol. 13, p. 945129, Aug. 2022, doi: 10.3389/fimmu.2022.945129.

[16] M. G. Alexandrow, L. J. Song, S. Altiok, J. Gray, E. B. Haura, and N. B. Kumar, “Curcumin: a novel Stat3 pathway inhibitor for chemoprevention of lung cancer,” *Eur. J. Cancer Prev.*, vol. 21, no. 5, pp. 407–412, Sep. 2012, doi: 10.1097/CEJ.0b013e32834ef194.