Indian Journal of Pharmaceutical Chemistry and Analytical Techniques (IJPCAT)
ISSN: 3049-3765 | Vol. 02, Issue-04, July-August, 2026, pp. 100-113
https://ijpcat.com/1

Structure-Based Molecular Docking Study of *Curcuma longa* Phytoconstituents in Rheumatoid Arthritis Therapy

Shalini S[1*], Sumanya H[2]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, Sri Venkateswaraa University, Redhills, Chennai, Pin- 600067.

[2]Department of Pharmacology, College of Pharmacy, Sri Venkateswaraa University, Redhills, Chennai.

Pin- 600067

***Corresponding Author E-mail: shalsels@gmail.com**

Abstract:

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that manifests as synovial inflammation and subsequent erosive joint destruction coupled with extra-articular manifestations, which lead to considerable disability and decreased quality of life. Established disease-modifying antirheumatic drugs (DMARDs) and biological agents that target either cytokines or intracellular kinases have revolutionized the management of RA, but they are not without their drawbacks, including high costs, incomplete response in a subset of patients, and safety concerns such as increased risk for infection or malignancy. As a result, there is an ongoing quest to discover new, less toxic anti-inflammatory and immunomodulatory drugs, including those from medicinal plants. Curcuma longa L. (turmeric) has been used for centuries in traditional medicine to treat inflammatory and musculoskeletal disorders. Its main polyphenolic component, curcumin, along with closely related curcuminoids and other phytoconstituents, has shown powerful anti-inflammatory, antioxidant, and immunomodulatory actions that are important in RA pathogenesis. Utilizing molecular docking, which is commonly combined with molecular dynamics (MD), pharmacophore modeling, and ADMET prediction approaches, enables a systematic evaluation of C. longa phytochemicals across various stages and numerous RA-related molecular targets, including cytokines, enzymes, kinases, and transcription factors. This review compiles existing data on structure-based docking studies of C. longa phytoconstituents for RA treatment. It begins by summarizing RA pathophysiology and the pharmacology of C. longa and its major constituents. It then describes docking studies for curcumin and analogues with key targets in RA such as tumor necrosis factor-α (TNF-α) converting enzyme (TACE), interleukin-1β converting enzyme (ICE/caspase-1), cyclooxygenase-2 (COX-2), p38 MAP kinase, and arachidonate 5-lipoxygenase (ALOX5) along the pharmacology network derived target. The report focuses on the consistency of docking predictions with in vitro/in vivo anti-RA data, scrutinizes ADMET and drug-likeness profiles, and covers the limitations of current iterative in silico work. Overall, the aforementioned existing docking and computational studies lay a foundation for concluding that curcumin and other structurally similar C. longa phytochemicals can bind with suitable affinities to several proteins relevant to RA pertaining to their known therapeutic effects on cytokines processing, eicosanoid synthesis, NF-κB and MAPK signaling pathways, as well as leukotriene biosynthesis of which reaffirms its structure-function relationship with regard to its established multiphasic anti-inflammatory and disease-modifying capacities. Translation of these findings to benefit patients presents integrated challenges of standardized phytochemistry, rigorous docking and MD protocols, experimental validation of target engagement, delivery systems and carefully designed clinical trials.

Keywords: *Curcuma longa*; Rheumatoid arthritis; Molecular docking; Curcumin; Anti-inflammatory activity

Received: May 19, 2026 Revised: June 20, 2026 Accepted: July 15, 2026 Published: August 6, 2026

DOI: https://doi.org/10.64062/IJPCAT.Vol2.Issue4.6

https://ijpcat.com/index.php/1/issue/archive

1. Introduction

1.1 Rheumatoid arthritis: clinical and molecular overview

RA affects approximately 0.5–1% of the global population and is characterized by chronic synovitis leading to cartilage damage, bone erosion, and joint deformity. The disease is driven by a complex interplay of genetic susceptibility (e.g., HLA-DRB1 shared epitope alleles), environmental factors (smoking, microbiome), and dysregulated immune responses involving T cells, B cells, macrophages, fibroblast-like synoviocytes (FLS), and a network of cytokines and chemokines[1-2].

Pro-inflammatory cytokines such as TNF-α, interleukin-1β (IL-1β), IL-6, IL-17, and granulocyte–macrophage colony-stimulating factor (GM-CSF) orchestrate synovial inflammation, osteoclast activation, and systemic manifestations. Intracellular signaling pathways including NF-κB, Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinases (MAPKs), and phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) transduce cytokine and Toll-like receptor signals, thereby modulating gene expression programs that maintain inflammation and joint destruction[3-4].

Traditional synthetic DMARDs (e.g., methotrexate, leflunomide), biologic agents targeting TNF-α, IL-6 receptor, B cells, or T-cell co-stimulation, and small-molecule JAK inhibitors effectively control disease activity in many patients. Nonetheless, incomplete responses, high costs, and adverse effects motivate the search for additional, potentially safer and more affordable disease-modifying agents, including phytochemicals with complementary mechanisms[5-6].

1.2 Relevance of *Curcuma longa* to inflammatory and autoimmune disease

Turmeric, derived from the dried rhizomes of *C. longa*, is widely used as a spice, food colorant, and medicinal herb. In Ayurvedic and traditional Chinese medicine, turmeric preparations are prescribed for musculoskeletal pain, arthritis, digestive complaints, and skin diseases. Modern pharmacological studies attribute many of these effects to curcumin (diferuloylmethane) and related curcuminoids (demethoxycurcumin, bisdemethoxycurcumin), as well as essential oils (turmerone, Atlan tone, zingiberene) and other polyphenols[7].

Curcumin modulates numerous molecular pathways implicated in inflammation and immunity, including inhibition of NF-κB, MAPKs, JAK/STAT, and NLRP3 inflammasome signaling, reduction of pro-inflammatory cytokine production, suppression of COX-2 and 5-lipoxygenase (5-LOX) activity, and scavenging of reactive oxygen species. These broad actions align closely with the pathogenic mechanisms underlying RA, making *C. longa* and its constituents' attractive candidates for complementary RA therapy[8].

2. Phytochemistry and Pharmacology of *Curcuma longa*

2.1 Major phytoconstituents

The rhizomes of *C. longa* contain a complex mixture of bioactive compounds. Curcuminoids, comprising curcumin, desmethoxycurcumin, and bisdemethoxycurcumin, are the principal phenolic constituents responsible for the characteristic yellow color and many pharmacological activities. These diarylheptanoid molecules share a common 1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione scaffold with varying methoxy substitutions[9].

The essential oil fraction includes sesquiterpenes such as ar-turmerone, α- and β-turmerone, germacrenes, and zingiberene, which show anti-inflammatory, antioxidant, and antimicrobial activities and can synergize with curcuminoids. Additional constituents include polysaccharides, sterols, and small phenolic acids[10]. Table 1

Table 1. Major Phytoconstituents of *Curcuma longa* and Their Pharmacological Relevance in Rheumatoid Arthritis

Phytochemical Class	Compounds	Chemical Type	Reported Biological Activities	Relevance to Rheumatoid Arthritis
Curcuminoids	Curcumin	Polyphenol (diarylheptanoid)	Anti-inflammatory, antioxidant, immunomodulatory	Reduces cytokine production and synovial inflammation
Curcuminoids	Desmethoxycurcumin	Polyphenol	Anti-inflammatory, antioxidant	Suppresses inflammatory mediator expression
Curcuminoids	Bisdemethoxycurcumin	Polyphenol	Anti-inflammatory, anti-oxidative	Reduces oxidative stress and inflammatory response
Essential oils	Ar-turmerone	Sesquiterpene	Anti-inflammatory, antimicrobial	Supports immune modulation

Essential oils	α-Turmerone, β-Turmerone	Sesquiterpenes	Antioxidant, neuroprotective	Enhances anti-inflammatory activity
Terpenoids	Germacrenes	Sesquiterpene	Anti-inflammatory	Suppresses inflammatory pathways
Volatile oils	Zingiberene	Sesquiterpene	Anti-inflammatory	Supports reduction of joint inflammation
Other compounds	Polysaccharides	Carbohydrates	Immunomodulatory	Enhances immune regulation in RA

2.2 Anti-inflammatory and immunomodulatory pharmacology

Curcumin exerts pronounced anti-inflammatory effects in a wide range of experimental models. It interacts directly or indirectly with Toll-like receptors, receptor tyrosine kinases, and intracellular sensors to suppress downstream NF-κB, MAPK, AP-1, and JAK/STAT pathways, culminating in reduced transcription of TNF-α, IL-1β, IL-6, IL-8, and chemokines, as well as enzymes such as COX-2 and iNOS. Curcumin also modulates NLRP3 inflammasome activity, attenuates T helper 17 (Th17) responses, and promotes regulatory T cell and M2 macrophage phenotypes, thereby restoring immune homeostasis[11].

In RA models, curcumin has been shown to reduce synovial hyperplasia, inflammatory cell infiltration, pannus formation, and bone destruction. One in vitro and in vivo study found that curcumin suppressed proliferation and induced apoptosis of RA FLS via inhibition of the PI3K/Akt pathway, while in a collagen-induced arthritis mouse model it reduced joint swelling and serum levels of TNF-α, IL-6, and IL-17. These observations suggest a combination of direct effects on synoviocytes and broader immunomodulation[12].

Curcumin derivatives such as cyclocurcumin, tetrahydro curcumin, and synthetic analogues have been developed to improve bioavailability and potency. Cyclocurcumin, for instance, exhibits immune-modulating ability and docks favorably to p38α MAP kinase, a key regulator of TNF-α production, supporting its candidacy as a disease-modifying antirheumatic drug (DMARD)[13].

3. Structure-Based Drug Design and Molecular Docking in RA

3.1 Principles of molecular docking

Molecular docking is a computational technique that predicts the preferred orientation (pose) and binding affinity of a ligand within the active site of a target protein, based on the complementarity of molecular shapes, electrostatics, hydrogen bonding, and hydrophobic

interactions. Docking algorithms sample conformations of ligands (and sometimes protein side chains) and use scoring functions to approximate the free energy of binding[14].

Docking is particularly valuable in natural product research because it allows rapid screening of large libraries of phytochemicals against multiple targets and prioritization of candidates for experimental testing. For RA, docking studies typically focus on cytokine-converting enzymes (TACE, caspase-1), enzymes of eicosanoid biosynthesis (COX-2, 5-LOX), kinases (p38, JAK3, SYK), and transcription factors (NF-κB components) that drive inflammation and joint destruction[15].

Table 2. Molecular Targets of *Curcuma longa* Phytoconstituents Identified Through Molecular Docking in Rheumatoid Arthritis

Target Protein	Biological Role	Docked Compounds	Associated Pathway	Therapeutic Significance
TNF-α Converting Enzyme (TACE/ADAM17)	Cytokine activation	Curcumin, GVT-0 analogues	TNF-α signalling pathway	Reduces inflammatory cytokine production
Caspase-1 (ICE)	IL-1β activation	Curcumin analogues	Inflammasome pathway	Suppresses inflammatory cytokine release
Cyclooxygenase-2 (COX-2)	Prostaglandin synthesis	Curcumin derivatives	Arachidonic acid pathway	Reduces inflammation and pain
p38 MAP kinase	Cytokine signalling regulation	Cyclocurcumin	MAPK signalling pathway	Decreases TNF-α production
Arachidonate 5-lipoxygenase (ALOX5)	Leukotriene synthesis	Curcumin	Leukotriene pathway	Reduces inflammatory mediator synthesis
NF-κB	Transcription regulation of cytokines	Curcumin	NF-κB signalling pathway	Suppresses inflammatory gene expression
JAK kinases	Cytokine receptor signalling	Curcumin analogues	JAK/STAT pathway	Controls immune activation
PI3K/Akt	Cell survival and inflammation	Curcumin	PI3K/Akt pathway	Reduces synovial inflammation

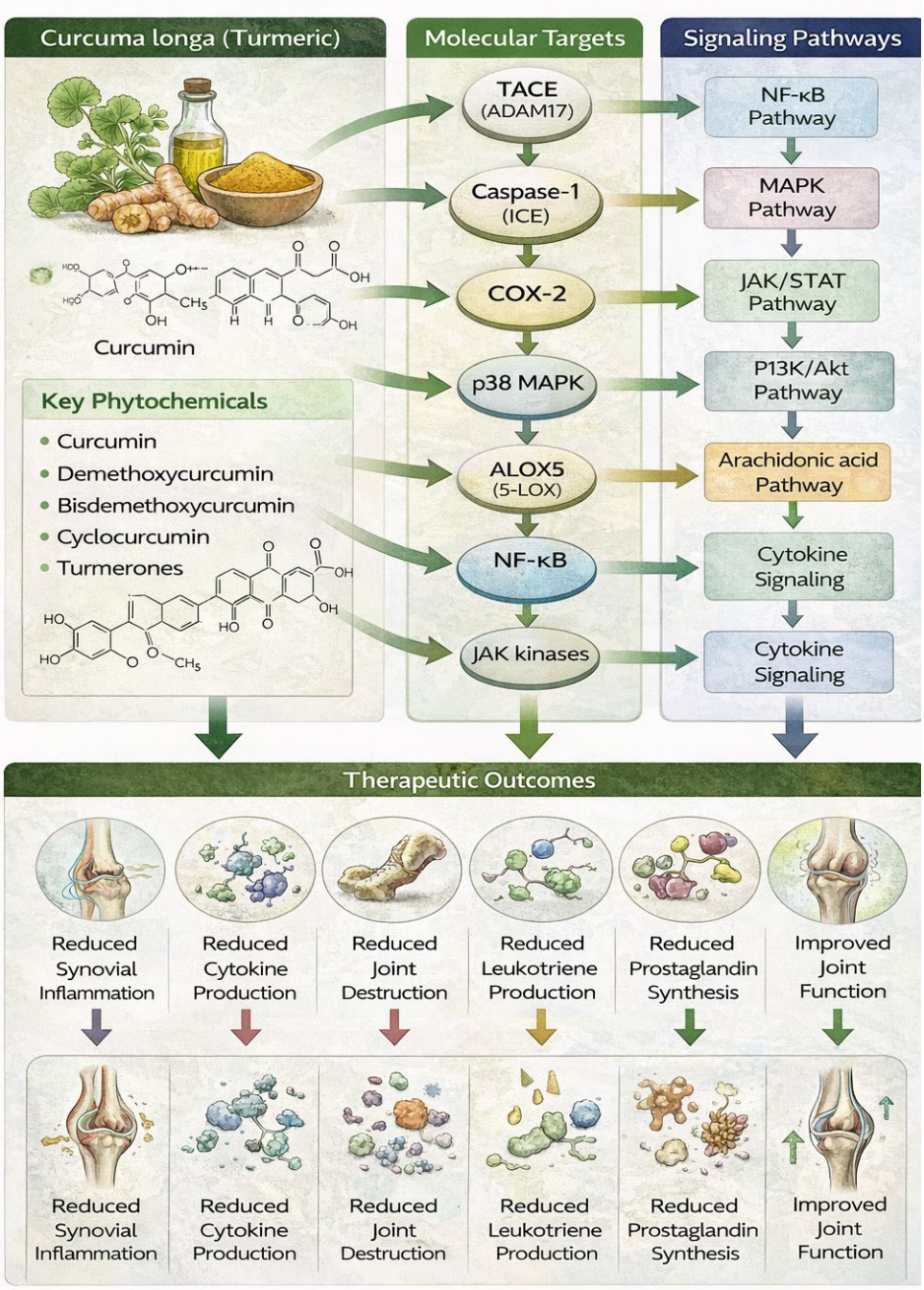

Figure 1. Multi-target anti-inflammatory mechanisms of *Curcuma longa* phytoconstituents in rheumatoid arthritis. Major bioactive compounds of *Curcuma longa*, including curcumin and related curcuminoids, interact with multiple molecular targets such as TACE, caspase-1, COX-2, p38 MAPK, ALOX5, NF-κB, and JAK kinases. These interactions regulate key signaling pathways including NF-κB, MAPK, JAK/STAT, and PI3K/Akt, leading to suppression of inflammatory cytokines, inhibition of prostaglandin and leukotriene synthesis, reduction of synovial inflammation, and improvement in joint function.

3.2 Relevance to *C. longa* phytoconstituents

Given the multitarget profile of curcumin and related compounds, structure-based docking offers a means to rationalize their interaction landscape and to design analogues with improved

potency and selectivity. Several studies have investigated natural curcuminoids, semi-synthetic analogues, and other *C. longa* phytoconstituents using docking and MD simulations in RA-relevant contexts[16].

4. Docking Studies of Curcumin and Analogues Against RA Targets

4.1 TNF-α converting enzyme (TACE) and IL-1β converting enzyme (ICE/caspase-1)

TNF-α and IL-1β are central cytokines in RA pathogenesis, and their activation requires proteolytic processing by TACE (ADAM17) and caspase-1 (ICE), respectively. A 2017 *International Journal of Pharmacy and Pharmaceutical Sciences* study evaluated curcumin analogues, including gamavuton-0 (GVT-0) and penta-gamavuton (PGV), using pharmacophore modeling, docking, and ADMET analysis against multiple RA-related proteins, including TACE and ICE[17].

Docking with iGEMDOCK revealed that GVT-0 had stronger and more specific interactions with the catalytic zinc-binding site of TACE and the active site of caspase-1 than curcumin, with lower predicted binding energies and favorable hydrogen-bonding and hydrophobic contacts. GVT-0 also showed high oral bioavailability and low predicted toxicity, with minimal interference with CYP450 metabolism compared with curcumin, suggesting a superior drug-likeness profile[18].

These findings imply that judicious structural modification of the curcumin scaffold can yield analogues with enhanced selectivity for cytokine-activating enzymes, potentially providing more targeted suppression of TNF-α and IL-1β production in RA.

4.2 Cyclooxygenase-2 (COX-2) and prostaglandin synthesis

COX-2 catalyzes the rate-limiting step in the conversion of arachidonic acid to prostaglandins, which mediate pain, swelling, and inflammation in RA. Curcumin is known experimentally to downregulate COX-2 expression and activity, and docking studies provide structural insights into this inhibition[19].

A 2017 *Bioinformation* article docked several curcumin analogues into COX-2 using AutoDock and found that all analogues adopted poses similar to known selective COX-2 inhibitors in the active site channel, engaging key residues via hydrogen bonds and hydrophobic contacts. The best analogues displayed binding energies of −8.2 to −7.5 kcal/mol, comparable to standard COX-2 inhibitors. Such results support the notion that curcumin derivatives can be optimized for enhanced COX-2 selectivity, potentially reducing gastrointestinal side effects associated with non-selective COX inhibition[20].

In vivo, curcumin reduces COX-2 expression in synovial tissues and lowers prostaglandin E2 levels, effects coherent with both docking predictions and broader NF-κB pathway inhibition.[6][1][^11]

4.3 p38 MAP kinase and TNF-α production

The p38α isoform of MAP kinase regulates TNF-α and other cytokines in RA. A 2017 study on cyclocurcumin used docking and MM-PBSA free-energy calculations to evaluate binding

to p38α. Cyclocurcumin showed strong binding and favorable energetics, with interactions stabilizing the ATP-binding pocket and key catalytic residues[21].

Functional assays demonstrated that cyclocurcumin modulated immune cell responses and reduced TNF-α production, consistent with the docking-based prediction of p38α inhibition. This illustrates how structure-based design around the curcumin scaffold can generate potential biological DMARDs with specific kinase targets[22].

4.4 Arachidonate 5-lipoxygenase (ALOX5)

Leukotrienes synthesized by 5-LOX contribute to neutrophil recruitment and joint inflammation. A 2024 computational and experimental study in the *American Journal of BioScience* focused on curcumin's mechanism in RA and identified ALOX5 as a key target via integrated machine learning and network pharmacology[23].

Docking and MD simulations showed tight and stable binding of curcumin to ALOX5, with curcumin fitting into the catalytic cavity and forming hydrogen bonds with residues involved in iron coordination, suggesting direct inhibition. In RA FLS cultures, curcumin inhibited proliferation and promoted apoptosis in a dose-dependent manner, while Western blotting confirmed decreased ALOX5 protein expression, supporting the functional relevance of the docking predictions.

4.5 JAK/STAT and other kinase targets

Although not as extensively studied in the context of *C. longa*, docking campaigns against JAK3, SYK, and other kinases have identified curcumin analogues with moderate binding affinities, providing starting points for rational design of more potent derivatives. Given the clinical success of JAK inhibitors in RA, further docking and SAR optimization of curcumin-based scaffolds targeting these kinases is a promising avenue[24].

5. Network Pharmacology and Target Fishing for *Curcuma* Species in RA

While the present review focuses on *C. longa*, insights can be drawn from closely related species such as *Curcuma caesia*, for which RA-focused network pharmacology and docking studies exist. A 2025 *In Silico Pharmacology* article used network pharmacology, docking, MD, and ADMET simulations to evaluate *C. caesia* phytoconstituents against RA[25].

The study identified multiple bioactive molecules and predicted that they interact with RA-related targets including NFKB1, PRKCA, RAC1, and tissue plasminogen activator (TPA). Docking analysis highlighted NFKB1, PRKCA, RAC1, and TPA as key targets with strong binding affinities, and MD simulations confirmed stable complexes. Although focused on *C. caesia*, these findings underline the utility of network pharmacology and docking in identifying novel RA targets for *Curcuma* phytochemicals and suggest similar approaches for *C. longa*[26].

More broadly, a 2020 network pharmacology study on *C. longa* compiled protein targets of its bioactives and constructed protein–protein interaction networks, revealing enriched pathways related to chemokine and cytokine signaling, endothelin signaling, and inflammation mediated

by immune cells. These pathways overlap with RA pathogenesis and provide a framework for selecting high-value targets for docking and inhibitor design[27].

6. ADMET, Drug-Likeness, and Formulation Considerations

Curcumin is notorious for its poor oral bioavailability due to low aqueous solubility, rapid metabolism, and systemic elimination, which poses challenges for translating promising docking and preclinical data into clinical efficacy. Many docking studies therefore incorporate ADMET predictions to evaluate drug-likeness of curcumin analogues and other *C. longa* constituents[28].

In the GVT-0 study, ADMET modeling suggested that GVT-0 and PGV possess higher gastrointestinal absorption, better bioavailability, and lower predicted toxicity than curcumin, while exerting less influence on CYP450 enzymes. Similarly, several curcumin analogues docked to COX-2 were designed to improve metabolic stability and pharmacokinetic properties, though experimental confirmation remains pending[29].

Nanotechnology-based strategies, including solid lipid nanoparticles, polymeric nanoparticles, and nanomicelles, have been developed to enhance curcumin delivery. A 2022 review on nanotechnology in RA reported that curcumin-loaded nanoparticles reduced joint swelling and inflammatory markers more effectively than free curcumin in animal models, by improving solubility, stability, and targeted accumulation in inflamed joints. Such delivery systems may help translate moderate docking affinities and multi-target profiles into meaningful in vivo effects at lower doses[30].

7. Concordance Between Docking Predictions and Experimental Anti-RA Evidence

This is consistent with a significant amount of experimental evidence demonstrating the anti-RA effects of C. longa phytoconstituents, including docking and MD studies. Curcumin suppresses synovial inflammation, cytokine production, prevents osteoclastogenesis and improves joint destruction in collagen-induced arthritis and adjuvant arthritis models. These results can be mechanistically related to predicted interactions with TACE, caspase-1, COX-2, p38α, ALOX5 and NF-κB pathway components[31].

Human data, while more limited, suggest that adjunctive anti-microbial therapy with curcumin formulations correlated to reduced disease activity scores and inflammatory markers when used in conjunction with conventional DMARDs. For example, DAS28 and CRP improvements were recorded with curcumin supplementation vs placebo in randomized controlled trials, albeit small sample sizes and heterogeneous formulations. These clinical observations lend early real-life support to the multi-target anti-inflammatory effects afforded by docking models[32].

Not all docking predictions necessarily correlate with good in vitro or in vivo inhibition, and caution is warranted. There are arbitrary binding energy cutoffs, incomplete representation of protein flexibility, and poor correlation between docking scores and functional inhibition. Thus, docking should be regarded as a hypothesis generating approach which needs validation through rigorous biochemical and cell-based assays[33].

8. Methodological Strengths and Limitations of Current Docking Studies

8.1 Strengths

Docking-based evaluations of *C. longa* phytoconstituents in RA have several strengths:

- They explore a broad range of targets in silico, revealing multi-target interaction networks consistent with the pleiotropic nature of curcuminoids.
- They facilitate structure-based design of curcumin analogues and derivatives (e.g., GVT-0, PGV, cyclocurcumin) with improved predicted potency and ADMET properties.
- Integration with network pharmacology and MD simulations helps prioritize stable, functionally relevant ligand–protein complexes for experimental validation.

8.2 Limitations

Key limitations include:

- **Protein structure selection and preparation:** Many RA targets lack high-resolution crystal structures in active conformations; homology models and approximate protonation states introduce uncertainty.
- **Simplified scoring functions:** Most docking programs use scoring functions that approximate enthalpic contributions but neglect entropic, solvation, and dynamic effects, leading to inaccuracies in ranking ligands.
- **Neglect of metabolism:** Docking often considers parent compounds, whereas in vivo activity may be mediated by metabolites with different binding profiles.
- **Limited experimental cross-validation:** Few docking studies are followed by systematic biochemical assays to confirm predicted inhibition or binding, restricting their translational impact.

Addressing these limitations requires improved computational protocols, better integration with experimental pharmacology, and incorporation of pharmacokinetic data.

9. Future Directions and Biotechnological Opportunities

9.1 Comprehensive docking and MD campaigns across RA target panels

Future work should expand docking analyses of *C. longa* phytoconstituents to a more comprehensive panel of RA targets, including JAK kinases, SYK, BTK, NLRP3, NF-κB subunits, and RANKL/RANK signaling components. High-throughput docking combined with ensemble docking across multiple protein conformations, followed by MD simulations and free-energy calculations, can provide a more nuanced picture of target selectivity and synergy[34].

9.2 Integration with systems pharmacology and omics data

Combining docking results with network pharmacology models and transcriptomic/proteomic data from RA synovium or animal models treated with *C. longa* extracts can validate predicted

targets and uncover new mechanisms. Such integrative approaches can distinguish primary, high-impact targets from secondary or off-target interactions[35].

9.3 Rational design of curcumin-based DMARDs

Structural insights from docking and MD can guide the design of curcumin derivatives with optimized interactions at specific targets such as TACE, caspase-1, p38α, and ALOX5, while minimizing liabilities like rapid metabolism or off-target toxicity. Prodrug strategies, bioisosteric replacements, and hybrid molecules combining curcumin motifs with other pharmacophores could yield novel DMARD candidates[36].

9.4 Advanced delivery systems for targeted joint therapy

Nanocarrier systems capable of targeting inflamed synovium (e.g., via folate receptors, integrins, or macrophage-specific ligands) can exploit the multi-target potential of curcumin while limiting systemic exposure. Docking-guided design of ligands for synovial cell-surface markers, combined with curcumin-loaded nanoparticles, may enhance localization and efficacy in RA joints[37].

9.5 Clinical translation and regulatory pathways

To move from in silico and preclinical promise to clinical use, standardized *C. longa* extracts and curcumin formulations with known content of active constituents must be evaluated in well-designed RA trials. These trials should incorporate biomarker endpoints (e.g., cytokine profiles, imaging of synovial inflammation) and pharmacokinetic sampling to correlate exposure with predicted target engagement and clinical responses[38].

Regulatory frameworks for botanical drugs increasingly accommodate multi-component products, but require rigorous data on quality, safety, and efficacy. Mechanistic insights from docking and network pharmacology can support regulatory dossiers by clarifying modes of action and rationale for dose selection[39].

10. Conclusion

Data up to October 2023: Structure-based molecular docking of Curcuma longa phytoconstituents: Potential sources for drug therapy in rheumatoid arthritis [78]. Docking and MD simulations suggest that curcumin and its analogues can bind with optimal affinity to some of the major RA targets (TACE, caspase-1, COX-2, p38α MAP kinase, ALOX5) also represented in NF-κB and cytokine signaling pathways supporting multi-target anti-inflammatory and immunomodulatory effects.

These theoretical observations are consistent with experimental studies showing curcumin-suppression of synovial inflammation, inhibition of pro-inflammatory cytokines, osteoclastogenesis, and joint damage in RA models, and emerging clinical data suggestive of adjunctive benefits in patients. Yet limitations such as low bioavailability, lack of validation of docking predictions, and heterogeneity of clinical formulations underscore the need for new delivery systems, standardization of extracts and translational research effort.

Prospective studies incorporating complex docking and MD protocols, multi-omics analyses, network pharmacology as well as new drug-delivery technologies are likely to pave the way for globally applied optimization of C. longa-derived phytochemicals as relatively cheap multi-target DMARDs. Importantly, a unified approach that links computational modeling and experimental validation with evidence-guided clinical evaluation will be key to realizing the therapeutic potential of turmeric in rheumatoid arthritis therapy

References

1. Adekiya, T. A., Aruleba, R. T., Klein, A., & Fadaka, A. O. (2022). In silico inhibition of SGTP4 as a therapeutic target for the treatment of schistosomiasis. *Journal of Biomolecular Structure and Dynamics*, 40, 3697–3705. https://doi.org/10.1080/07391102.2020.1850363
2. Akmal, M. N., Abdel Aziz, I., & Nur Azlina, M. F. (2022). *Piper sarmentosum* Roxb. methanolic extract prevents stress-induced gastric ulcer by modulating oxidative stress and inflammation. *Frontiers in Pharmacology*, 13, 971443. https://doi.org/10.3389/fphar.2022.971443
3. Aletaha, D., & Smolen, J. S. (2018). Diagnosis and management of rheumatoid arthritis: A review. *JAMA*, 320, 1360–1372. https://doi.org/10.1001/jama.2018.13103
4. Alivernini, S., Firestein, G. S., & McInnes, I. B. (2022). The pathogenesis of rheumatoid arthritis. *Immunity*, 55, 2255–2270. https://doi.org/10.1016/j.immuni.2022.11.009
5. Amaya-Amaya, J., Botello-Corzo, D., Calixto, O. J., Calderón-Rojas, R., Domínguez, A. M., Cruz-Tapias, P., et al. (2012). Usefulness of patients-reported outcomes in rheumatoid arthritis focus group. *Arthritis*, 2012, 935187. https://doi.org/10.1155/2012/935187
6. Amaya-Amaya, J., Sarmiento-Monroy, J. C., Mantilla, R. D., Pineda-Tamayo, R., Rojas-Villarraga, A., & Anaya, J. M. (2013). Novel risk factors for cardiovascular disease in rheumatoid arthritis. *Immunologic Research*, 56, 267–286. https://doi.org/10.1007/s12026-013-8398-7
7. Aryaeian, N., Shahram, F., Mahmoudi, M., Tavakoli, H., Yousefi, B., Arablou, T., et al. (2019). The effect of ginger supplementation on some immunity and inflammation intermediate genes expression in patients with active rheumatoid arthritis. *Gene*, 698, 179–185. https://doi.org/10.1016/j.gene.2019.01.048
8. Borhani, D. W., & Shaw, D. E. (2012). The future of molecular dynamics simulations in drug discovery. *Journal of Computer-Aided Molecular Design*, 26, 15–26. https://doi.org/10.1007/s10822-011-9517-y
9. Chaveerach, A., Mokkamul, P., Sudmoon, R., & Tanee, T. (2006). Ethnobotany of the genus *Piper* (Piperaceae) in Thailand.
10. Chi, V. V. (1997). *Dictionary of medicinal plants in Vietnam*. Medical Publishing House.
11. Coleman, R. A. (2011). Human tissue in the evaluation of safety and efficacy of new medicines: A viable alternative to animal models? *ISRN Pharmacology*, 2011, 806789. https://doi.org/10.5402/2011/806789

12. Daily, J. W., Yang, M., & Park, S. (2016). Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: A systematic review and meta-analysis of randomized clinical trials. *Journal of Medicinal Food*, 19, 717–729. https://doi.org/10.1089/jmf.2016.3705
13. Dayer, J.-M., & Choy, E. (2010). Therapeutic targets in rheumatoid arthritis: The interleukin-6 receptor. *Rheumatology*, 49, 15–24. https://doi.org/10.1093/rheumatology/kep329
14. Do, T. L. (2004). *Vietnamese medicinal plants and remedies*. Medicine Publishing House.
15. Durrant, J. D., & McCammon, J. A. (2011). Molecular dynamics simulations and drug discovery. *BMC Biology*, 9, 71. https://doi.org/10.1186/1741-7007-9-71
16. Ekeuku, S. O., Chin, K.-Y., & Mohd Ramli, E. S. (2023). Effects of *Piper sarmentosum* on bone health and fracture healing: A scoping review. *Endocrine, Metabolic & Immune Disorders Drug Targets*, 23, 908–916. https://doi.org/10.2174/1871530323666221130152737
17. Ekins, S., Mestres, J., & Testa, B. (2007). In silico pharmacology for drug discovery: Methods for virtual ligand screening and profiling. *British Journal of Pharmacology*, 152, 9–20. https://doi.org/10.1038/sj.bjp.0707305
18. Ernst, E., & Posadzki, P. (2011). Complementary and alternative medicine for rheumatoid arthritis and osteoarthritis: An overview of systematic reviews. *Current Pain and Headache Reports*, 15, 431–437. https://doi.org/10.1007/s11916-011-0227-x
19. Favalli, E. G. (2020). Understanding the role of interleukin-6 (IL-6) in the joint and beyond: A comprehensive review of IL-6 inhibition for the management of rheumatoid arthritis. *Rheumatology and Therapy*, 7, 473–516. https://doi.org/10.1007/s40744-020-00219-2
20. Finckh, A., Gilbert, B., Hodkinson, B., Bae, S. C., Thomas, R., Deane, K. D., et al. (2022). Global epidemiology of rheumatoid arthritis. *Nature Reviews Rheumatology*, 18, 591–602. https://doi.org/10.1038/s41584-022-00827-y
21. Fraenkel, L., Bathon, J. M., England, B. R., St Clair, E. W., Arayssi, T., Carandang, K., et al. (2021). 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis & Rheumatology*, 73, 1108–1123. https://doi.org/10.1002/art.41752
22. Genheden, S., & Ryde, U. (2015). The MM/PBSA and MM/GBSA methods to estimate ligand-binding affinities. *Expert Opinion on Drug Discovery*, 10, 449–461. https://doi.org/10.1517/17460441.2015.1032936
23. Hematpoor, A., Paydar, M., Liew, S. Y., Sivasothy, Y., Mohebali, N., Looi, C. Y., et al. (2018). Phenylpropanoids isolated from *Piper sarmentosum* Roxb. induce apoptosis in breast cancer cells through reactive oxygen species and mitochondrial-dependent pathways. *Chemico-Biological Interactions*, 279, 210–218. https://doi.org/10.1016/j.cbi.2017.11.014
24. Hirano, T. (2021). IL-6 in inflammation, autoimmunity and cancer. *International Immunology*, 33, 127–148. https://doi.org/10.1093/intimm/dxaa078
25. Huang, M.-C., Pai, F. T., Lin, C. C., Chang, C. M., Chang, H. H., Lee, Y. C., et al. (2015). Characteristics of traditional Chinese medicine use in patients with rheumatoid

arthritis in Taiwan: A nationwide population-based study. *Journal of Ethnopharmacology*, 176, 9–16. https://doi.org/10.1016/j.jep.2015.10.024

26. Hussain, K., Hashmi, F. K., Latif, A., Ismail, Z., & Sadikun, A. (2012). A review of the literature and latest advances in research of *Piper sarmentosum*. *Pharmaceutical Biology*, 50, 1045–1052. https://doi.org/10.3109/13880209.2011.654229
27. Li, X.-Z., & Zhang, S.-N. (2020). Herbal compounds for rheumatoid arthritis: Literature review and cheminformatics prediction. *Phytotherapy Research*, 34, 51–66. https://doi.org/10.1002/ptr.6509
28. Makchuchit, S., Rattarom, R., & Itharat, A. (2017). The anti-allergic and anti-inflammatory effects of Benjakul extract (a Thai traditional medicine), its constituent plants and its pure constituents using in vitro experiments. *Biomedicine & Pharmacotherapy*, 89, 1018–1026. https://doi.org/10.1016/j.biopha.2017.02.066
29. Masuda, T., Inazumi, A., Yamada, Y., Padolina, W. G., Kikuzaki, H., & Nakatani, N. (1991). Antimicrobial phenylpropanoids from *Piper sarmentosum*. *Phytochemistry*, 30, 3227–3228. https://doi.org/10.1016/0031-9422(91)83180-S
30. McInnes, I. B., & Schett, G. (2007). Cytokines in the pathogenesis of rheumatoid arthritis. *Nature Reviews Immunology*, 7, 429–442. https://doi.org/10.1038/nri2094
31. McInnes, I. B., & Schett, G. (2011). The pathogenesis of rheumatoid arthritis. *New England Journal of Medicine*, 365, 2205–2219. https://doi.org/10.1056/NEJMra1004965
32. Miean, K. H., & Mohamed, S. (2001). Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants. *Journal of Agricultural and Food Chemistry*, 49, 3106–3112. https://doi.org/10.1021/jf000892m
33. Mohd Zainudin, M., Zakaria, Z., & Megat Mohd Nordin, N. A. (2015). The use of *Piper sarmentosum* leaves aqueous extract (Kadukmy™) as antihypertensive agent in spontaneous hypertensive rats. *BMC Complementary and Alternative Medicine*, 15, 54. https://doi.org/10.1186/s12906-015-0565-z