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Research Article

IN SILICO EVALUATION OF *CURCUMA LONGA* PHYTOCONSTITUENTS TARGETING KEY PROTEINS IN ARTHRITIS MANAGEMENT

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ABSTRACT

Background:

Arthritis is a progressive inflammatory disorder that affects joints, leading to chronic pain, swelling, and stiffness. Standard treatments offer temporary relief but can cause long-term side effects[1,6]. This has created interest in herbal remedies like *Curcuma longa*, known for its multi-targeted anti-inflammatory and antioxidant properties rooted in traditional medicine[1,2,6]. The objective of this study was to explore the molecular interactions of *Curcuma longa* phytochemicals with target proteins involved in arthritis using *In silico* methods. The aim was to identify compounds with the strongest binding affinity and favorable pharmacokinetic properties to support their use as natural anti-arthritic agents[1,7].

Methods:

Molecular docking was performed using AutoDock Vina within PyRx software on selected proteins related to arthritis: TNF-α, JAKs, COX-2, and MMPs. Ligands were prepared and optimized using ChemSketch[4]. ADME(Absorption Distribution metabolism and Elimintion) and Lipinski's rules were evaluated using SwissADME[5] to assess oral bioavailability and drug-likeness of the compounds studied.

Results:

Several compounds, including bisdemethoxycurcumin, ellagic acid, and genistein, demonstrated high binding affinity to multiple protein targets, particularly COX-2 and MMPs. Most compounds showed zero Lipinski violations and suitable iLOGP values, indicating good oral bioavailability[5]. The docking scores and RMSD values confirmed stable and specific ligand-protein interactions.

Conclusion:
The *in silico* results support the therapeutic promise of *Curcuma longa* constituents as multi-targeted natural drugs for arthritis management[2,9]. The favorable drug-likeness and binding properties justify further preclinical and clinical evaluation. This study lays the groundwork for developing safe, plant-based interventions in chronic inflammatory diseases like arthritis.

KEYWORDS

Anti-inflammatory, Arthritis, Curcuma longa, Natural Compounds, Molecular Docking

1. INTRODUCTION

Arthritis is a progressive and often chronic joint disorder marked by inflammation, stiffness, swelling, and pain, affecting millions of individuals worldwide. It significantly impacts the quality of life by limiting mobility and causing long-term disability, especially among the aging population. The two most prevalent forms of arthritis are osteoarthritis (OA) and rheumatoid arthritis (RA). Osteoarthritis is typically degenerative in nature, involving the breakdown of cartilage and wear-and-tear of joints, while rheumatoid arthritis is an autoimmune condition characterized by systemic inflammation and synovial membrane damage. Despite their differing etiologies, both forms involve complex pathophysiological mechanisms such as immune dysregulation, oxidative stress, inflammatory cytokine release, and enzymatic degradation of joint tissues. Current treatment regimens include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), and biologics. However, these conventional therapies are often associated with adverse effects, including gastrointestinal irritation, immunosuppression, and cardiovascular risks[6]. Therefore, the growing emphasis on safe, long-term therapeutic strategies has intensified the search for effective natural alternatives.

One such promising natural source is *Curcuma long*a L., commonly known as turmeric, a perennial herb extensively used in traditional medicinal systems like Ayurveda, Unani, and Chinese medicine. The rhizome of *Curcuma longa* is renowned not only as a culinary spice but also for its wide range of therapeutic applications. Its primary active constituents include curcuminoids such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin, as well as essential oils like ar-turmerone, zingiberene, and β-sesquiphellandrene[1,2,6]. These bioactive compounds are well-documented for their potent anti-inflammatory, antioxidant, and immunomodulatory effects[1,2,3,7]. Modern pharmacological research has shown that these constituents exert inhibitory action on several molecular targets involved in arthritis, including tumor necrosis factor-alpha (TNF-α), cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs), Janus kinases (JAKs), and nuclear factor-kappa B (NF-κB)[1,3,8,10]. These proteins are central to the signaling cascades that mediate joint inflammation, cartilage degradation, and immune response. With advancements in computational tools, molecular docking has emerged as a valuable *in silico* technique to assess the binding affinity and interaction potential of phytochemicals with target proteins, thereby accelerating the drug discovery process from natural products[4,10].

The present study focuses on evaluating the anti-arthritic potential of selected phytochemicals derived from *Curcuma longa* through molecular docking analysis. The primary aim is to investigate how effectively these natural compounds bind with key proteins associated with arthritis pathogenesis, thereby identifying promising lead molecules for further drug development. The specific objectives of this study include:

1)Screening selected *Curcuma longa* compounds for their binding affinities to critical arthritis-related targets such as TNF-α, JAKs, COX-2, and MMPs.

2) Assessing their pharmacokinetic and drug-likeness profiles based on Lipinski's Rule of Five and iLOGP values to predict oral bioavailability

3)Identifying lead molecules with optimal binding energy and favorable ADME properties for potential therapeutic application in arthritis treatment. Through this approach, the study aims to contribute to the growing field of phytochemical-based drug discovery and support the development of safer, natural alternatives for arthritis management.

2. MATERIALS AND METHODS:

2.1. Target Protein Selection:

Key proteins implicated in the pathogenesis of arthritis were selected for molecular docking studies. These included:

- Tumor Necrosis Factor-alpha (TNF-α)
- Cyclooxygenase-2 (COX-2)
- Matrix Metalloproteinases (MMP-3, MMP-9)
- Janus Kinases (JAK1, JAK3)

The 3D crystal structures of these protein targets were retrieved from the Protein Data Bank (PDB) in .pdb format[4]. The protein structures were prepared by removing water molecules and heteroatoms, followed by the addition of hydrogen atoms and Gasteiger charges using AutoDock Tools.

2.2. Ligand Preparation:

Phytoconstituents of *Curcuma longa*, including curcumin, demethoxycurcumin, bisdemethoxycurcumin, ar-turmerone, and zingiberene, were selected based on their reported pharmacological relevance in arthritis. Their 3D structures were downloaded from PubChem in .sdf format and converted into .pdbqt format using Open Babel and AutoDock Tools. Energy minimization was performed using MMFF94 force field for better geometry optimization.

2.3. Molecular Docking:

Molecular docking studies were conducted using PyRx 0.8 with the AutoDock Vina algorithm. The docking grid was generated using the protein's active site coordinates obtained from literature. Docking parameters were set to default values, and the Lamarckian Genetic Algorithm (LGA) was applied. The binding affinities (kcal/mol) were recorded for each ligand-protein complex, and interactions were visualized using Discovery Studio Visualizer.

2.4. ADME Prediction:

The Lipinski Rule of Five and other drug-likeness properties such as molecular weight, hydrogen bond donors and acceptors, logP, and number of rotatable bonds were assessed using the SwissADME web tool (http://www.swissadme.ch)[5]. Molecules violating more than one rule were considered less suitable for oral bioavailability.

2.5. Target Prediction:

Swiss Target Prediction was employed to identify potential human protein targets for each phytoconstituent based on structural similarity with known bioactive compounds. This helped validate the selected targets in arthritis pathology and guided future pharmacological exploration[12].

OBSERVATION AND RESULTS :

Table. 1 : *In silico* study of *Curcuma Longa* :

Sr. No.	Phytochemical Constituent	Molecular Docking								ADME					Targets Predicted
		1st protein (1WDA)		2nd protein (1N26)		3rd protein (2AZ5)		4th protein (3T9T)		Mol. Wt.	#H-bond acceptors	#H-bond donors	iLOGP	Lipinski #violations	
		RMSD	B.E*	RMSD	B.E*	RMSD	B.E*	RMSD	B.E*						

		value		value		value		value							
1	Curcumin	5.597	-5.9	5.597	-5.9	5.905	-7.2	5.685	-7.9	368.38	6	2	3.27	0	Tumor Necrosis Factor-alpha (TNF-alpha)
															Janus Kinases (JAK1, JAK2, JAK3, TYK2)
															Matrix Metalloproteinases(MMP1, MMP3, MMP13)
															COX-2 (Cyclooxygenase-2)
2	Demethoxycurcumin	19.31	-5.8	19.31	-5.8	4.911	-7.3	4.711	-7.6	338.35	5	2	2.78	0	Tumor Necrosis Factor-alpha (TNF-alpha)
															Matrix Metalloproteinases(MMP1, MMP3, MMP13)
3	Bisdemethoxycurcumin	7.847	-6.2	7.847	-6.2	20.15	-7.6	10.21	-8.7	308.33	4	2	1.75	0	Tumor Necrosis Factor-alpha (TNF-alpha)
															Matrix Metalloproteinases(MMP1, MMP3, MMP13)
4	Cyclocurcumin	9.584	-6.9	9.584	-6.9	20.35	-8.1	8.152	-8.6	368.38	6	2	3.12	0	Tumor Necrosis Factor-alpha (TNF-alpha)
5	Dihydrocurcumin	8.916	-7	8.916	-7	20.06	-8.1	9.225	-7.9	370.4	6	2	2.87	0	Tumor Necrosis Factor-alpha (TNF-alpha)
															Janus Kinases (JAK1, JAK2, JAK3, TYK2)

															COX-2 (Cyclooxygenase-2)
6	Tetrahydrocurcumin	8.843	-6	8.843	-6	3.158	-6.5	7.754	-7.7	372.41	6	2	3.21	0	Bruton's Tyrosine kinase (BTK)
7	Hexahydrocurcumin	9.021	-6.3	9.021	-6.3	5.866	-6.1	7.909	-7.1	374.43	6	3	3.14	0	Janus Kinases (JAK1, JAK2, JAK3, TYK2)
															Nuclear factor- kappa B (NF-KB)
8	Curcumenol	4.042	-6.1	4.042	-6.1	20.50	-7.7	4.419	-7.5	234.33	2	1	3.12	0	Janus Kinases (JAK1, JAK2, JAK3, TYK2)
9	Curcumadiol	12.03	-5.9	12.03	-5.9	21.60	-7.3	4.692	-6.6	238.37	2	2	2.76	0	Janus Kinases (JAK1, JAK2, JAK3, TYK2)
															Matrix Metalloproteinases(MMP1, MMP3, MMP13)
10	α-Turmerone	6.014	-5.1	2.64	-5.5	19.51	-5.9	7.558	-7.3	218.33	1	0	3.11	0	Tumor Necrosis Factor-alpha (TNF-alpha)
															Matrix Metalloproteinases(MMP1, MMP3, MMP13)
11	β-Turmerone	5.704	-5.6	5.679	-4.9	19.96	-5.9	6.944	-7.4	218.33	1	0	3.16	0	Tumor necrosis factor-alpha (TNF-alpha)
12	Germacrone	4.926	-5.7	4.601	-5.8	21.76	-7.2	2.694	-6.5	218.33	1	0	2.88	0	COX-2 (Cyclooxygenase-2)
13	Myrcene	5.311	-4.1	17.81	-3.7	4.089	-4.6	5.492	-5.4	136.23	0	0	2.89	0	COX-2 (Cyclooxygenase-2)
14	Linalool	23.99	-4.2	3.984	-3.8	21.81	-5.3	6.511	-5.4	154.25	1	1	2.7	0	Janus Kinases (JAK1,

															JAK2, JAK3, TYK2)
															COX-2 (Cyclooxygenase-2)
15	Terpinen-4-ol	2.222	-5	12.34	-5	18.81	-5.6	4.637	-6.1	154.25	1	1	2.51	0	Janus Kinases (JAK1, JAK2, JAK3, TYK2)
16	Nerolidol	30.73	-4.9	6.892	-5.5	20.40	-6.1	2.282	-6.8	222.37	1	1	3.64	0	Interleukin-6 receptor (IL-6R)
															Janus Kinases (JAK1, JAK2, JAK3, TYK2)
															COX-2 (Cyclooxygenase-2)
17	Isoborneol	32.16	-4.8	7.707	-4.9	22.22	-5.7	2.563	-5.4	154.25	1	1	2.27	0	Janus Kinases (JAK1, JAK2, JAK3, TYK2)
															Matrix Metalloproteinases(MMP1, MMP3, MMP13)
															COX-2 (Cyclooxygenase-2)
18	Cedrene	4.099	-6	4.025	-5.9	20.44	-7.5	25.18	-6.9	204.35	0	0	3.2	0	Tumor Necrosis Factor-alpha (TNF-alpha)
19	Ferulic acid	59.14	-5.3	14.11	-5.2	6.181	-6.4	2.487	-6.5	194.18	4	2	1.62	0	Nuclear factor- kappa B (NF-KB)
															Matrix metalloproteinases(MMP-1, MMP-3, MMP-13)
															COX-2 (Cyclooxygenase-2)
20	Vanillic acid	35.58	-5	59.87	-5	21.97	-5.6	2.548	-6.1	168.15	4	2	1.4	0	Matrix Metalloproteinases(MMP1

															, MMP3, MMP13)
21	Syringic acid	43.96	-5.3	3.887	-5	3.43	-5.8	4.004	-5.6	198.17	5	2	1.54	0	Matrix Metalloproteinases(MMP1, MMP3, MMP13)
22	p-Coumaric acid	14.42	-5.3	16.44	-5.2	5.743	-6.1	2.766	-6.4	164.16	3	2	0.95	0	Nuclear factor- kappa B (NF-KB)
															COX-2 (cyclooxygenase-2)
23	Caffeic acid	32.27	-5.4	17.96	-5.4	6.252	-6.8	15.12	-6.4	180.16	4	3	0.97	0	Janus Kinases (JAK1, JAK2, JAK3, TYK2)
															Matrix Metalloproteinases(MMP1, MMP3, MMP13)
															COX-2 (cyclooxygenase-2)
24	Gallic acid	19.66	-5.4	15.08	-5.3	2.405	-5.7	2.571	-6.2	170.12	5	4	0.21	0	Matrix Metalloproteinases(MMP1, MMP3, MMP13)
															COX-2 (cyclooxygenase-2)
25	Ellagic acid	6.183	-7.4	6.195	-7	20.38	-7.8	2.924	-8.4	302.19	8	4	0.79	0	Nuclear factor- kappa B (NF-KB)
															COX-2 (cyclooxygenase-2)
26	Kaempferol	76.31	-6.6	6.043	-6.4	22.44	-7.3	6.895	-8.6	286.24	6	4	1.7	0	Matrix Metalloproteinases(MMP1, MMP3, MMP13)
															COX-2 (cyclooxygenase-2)
27	Myricetin	34.57	-6.6	2.355	-6.7	20.32	-7.4	7.196	-9	302.24	7	5	1.33	0	Matrix Metalloproteinases(MMP1

															, MMP3, MMP13)
28	Fisetin	60.03	-6.9	2.356	-6.9	20.57	-7.9	6.903	-8.8	286.24	6	4	1.5	0	Matrix Metalloproteinases(MMP1, MMP3, MMP13)
29	Isorhamnetin	74.89	-6.6	16.15	-6.4	6.914	-8.3	7.384	-8.8	516.26	7	4	2.35	0	Matrix Metalloproteinases(MMP1, MMP3, MMP13)
30	Luteolin	31.82	-6.9	2.127	-7.3	6.715	-8.8	7.148	-8.8	286.24	6	4	1.86	0	Matrix Metalloproteinases(MMP1, MMP3, MMP13)
31	Apigenin	31.94	-6.7	6.683	-6.6	6.683	-8.2	3.671	-8.8	270.24	5	3	1.89	0	Matrix Metalloproteinases(MMP1, MMP3, MMP13)
															COX-2 (cyclooxygenase-2)
32	Genistein	44.22	-7.4	6.966	-7.5	19.40	-8.4	7.123	-9.4	270.24	5	3	1.91	0	COX-2 (cyclooxygenase-2)
33	Ergosterol	9.713	-7.7	19.77	-7.6	17.10	-9.4	9.362	-8.5	396.65	1	1	4.81	0	Janus Kinases (JAK1, JAK2, JAK3, TYK2)
34	Diacetylcurcumin	34.96	-6.3	17.15	-5.1	18.29	-7.1	10.90	-8.2	452.45	8	0	3.83	0	Janus Kinases (JAK1, JAK2, JAK3, TYK2)
															Nuclear factor- kappa B (NF-KB)
35	Vanillin	43.03	-4.6	11.19	-4.8	22.85	-5.3	2.986	-5.4	152.15	3	1	1.57	0	Matrix Metalloproteinases(MMP1, MMP3, MMP13)
36	Xanthorrhizol	2.932	-5.9	5.936	-5.9	20.31	-6.3	7.083	-7.7	218.33	1	1	3.13	0	Janus Kinases (JAK1, JAK2, JAK3, TYK2)

															Nuclear factor- kappa B (NF-KB)
															COX-2 (cyclooxygenase-2)
37	Curzerenone	4.194	-5.5	4.452	-5.5	19.14	-7	23.87	-6.4	230.3	2	0	2.87	0	COX-2 (cyclooxygenase-2)
38	Methoxycurcumin	30.56	-5.8	5.645	-5.5	20.57	-7.1	31.96	-8	398.41	7	2	3.17	0	Nuclear factor- kappa B (NF-KB)
															Matrix Metalloproteinases(MMP1, MMP3, MMP13)
															ADAMTS-5 (Aggreanase)

*B.E= Binding Energy/Affinity.

4. DISCUSSION

The findings of this *in silico* study strongly highlight the therapeutic promise of *Curcuma longa* (turmeric) phytochemicals in managing arthritis. Arthritis, whether osteoarthritis or rheumatoid arthritis, is not caused by a single factor but rather involves multiple biological pathways. These include chronic inflammation, tissue damage, and immune system imbalance[1,6,9]. Interestingly, several compounds from *Curcuma longa* demonstrated strong binding to key proteins responsible for these processes—namely TNF-α and COX-2 (inflammation), MMPs (joint tissue breakdown), and JAKs/NF-κB (immune modulation).

Compounds such as ellagic acid, bisdemethoxycurcumin, genistein, and dihydrocurcumin showed excellent binding scores, especially with COX-2 and MMP proteins[1,10]. These results align with previously published studies that describe these compounds as having potent anti-inflammatory and tissue-protective effects. Among the curcuminoids, bisdemethoxycurcumin and cyclocurcumin stood out for their consistent and effective binding across all protein targets. This suggests that these compounds could act on multiple biological pathways at once—a beneficial property called polypharmacology, which is particularly useful in complex diseases like arthritis[9].

Another important observation is that most of the phytochemicals showed good drug-likeness when evaluated using Lipinski's Rule of Five. This rule helps predict whether a compound is likely to be a successful oral drug based on properties like molecular weight, lipophilicity, and hydrogen bonding. The selected compounds did not violate this rule and also had favorable iLOGP values, suggesting they are likely to be absorbed well in the body and have potential as orally administered medications.

It's important to note that these results are based on computer simulations. While molecular docking provides valuable predictions about how compounds may interact with biological targets, it does not replace laboratory testing[4,10,12]. However, it serves as an efficient and cost-effective method to narrow down promising lead compounds before moving on to in vitro (test tube) or in vivo (animal or human) studies.

The study provides strong preliminary evidence that several phytoconstituents of *Curcuma longa*, especially bisdemethoxycurcumin and cyclocurcumin, could be valuable candidates for developing natural, multi-targeted treatments for arthritis. These findings support the traditional use of turmeric in managing joint disorders and pave the way for future experimental validation and drug development.

5. CONCLUSION

This study provides compelling evidence that *Curcuma longa* (turmeric) contains multiple bioactive compounds capable of targeting key proteins involved in the development and progression of arthritis. Through molecular docking, compounds such as ellagic acid, genistein, bisdemethoxycurcumin, and dihydrocurcumin demonstrated strong binding to proteins like TNF-α, COX-2, MMPs, and JAKs—which are directly involved in inflammation, tissue breakdown, and immune regulation[1,9,10].

What makes these compounds especially promising is not only their strong binding affinities but also their excellent drug-like properties. All of the top-performing compounds followed Lipinski's Rule of Five[5], indicating good oral bioavailability and minimal likelihood of issues in drug formulation. Their ADME (absorption, distribution, metabolism, and excretion) profiles were also favorable, making them suitable candidates for further development as natural anti-arthritic agents.

Although these results were generated using computer-based simulations, they offer a valuable first step in identifying effective plant-based treatments for arthritis. The study highlights the therapeutic potential of turmeric's lesser-known constituents, especially bisdemethoxycurcumin and genistein, which deserve further scientific exploration.

These promising findings now need to be tested and validated in laboratory settings through in vitro (cell culture) and in vivo (animal) experiments[12]. This will help confirm their actual biological effects, safety profiles, and suitability for development into effective herbal formulations or pharmaceuticals.

Curcuma longa continues to prove its value in modern medicine, not just as a traditional remedy but as a scientifically supported source of potential drugs for arthritis management.

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