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Molecular Docking Analysis Of Bioactive Phytocompounds From Cinnamomum Tamala Targeting Key Inflammatory Pathways In Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) constitutes a chronic autoimmune inflammatory disease delineated by enduring synovitis, progressive degeneration of cartilage and bone, as well as systemic complications. The investigation of plant-derived phytochemicals has been a focal point for their anti-inflammatory and immunomodulatory capabilities. Computational molecular docking serves as an expedited and economically viable methodology to forecast protein-ligand interactions and to prioritize candidates for therapeutic advancement.

In the present study, four phytocompounds extracted from Cinnamomum tamala such as Kaempferol, Quercetin, Phytol and Naringenin were employed in molecular docking assays against 13 pivotal inflammatory protein targets implicated in RA, which include AP-1, NF-κB, AKT, PI3K, MAPK-1, COX-2, LOX, TNF-α, IL-1β, IL-6, TLR-4, Glutaminase-1and MMP-1. The docking analyses were conducted utilizing ArgusLab version 4.0.1.

The results indicated that Phytol demonstrated the most robust overall binding affinities, particularly towards AP-1 (−16.23 kcal/mol) and COX-2 (−14.05 kcal/mol). Kaempferol and Quercetin exhibited notable affinities with COX-2, MAPK-1and cytokine-related targets, whereas Naringenin revealed strong interactions with AKT (−11.18 kcal/mol), IL-6 (−9.23 kcal/mol) and COX-2 (−9.39 kcal/mol). These findings imply that phytochemicals derived from C. tamala may function as potential multi-target anti-inflammatory agents, bearing significant therapeutic implications for the management of RA.

Keywords: *Rheumatoid arthritis, Molecular docking, Cinnamomum tamala, Kaempferol, Quercetin, Phytol, Naringenin, Anti-inflammatory*

INTRODUCTION

Rheumatoid arthritis (RA) constitutes a systemic, chronic and progressive autoimmune disorder which predominantly affects synovial joints, resulting in enduring inflammation, degradation of cartilage, erosion of bone and ultimately, functional impairment. On a global scale, RA impacts approximately 1% of the adult demographic, with a heightened incidence observed in females relative to males **(Smolen et al., 2018).** The pathogenesis of RA is intricate and multifaceted, encompassing the interaction of genetic predisposition, environmental stimuli and aberrant immune responses. The condition is characterized by the infiltration of activated T cells, B cells and macrophages into the synovial membrane, which subsequently secrete pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1βand IL-6. These cytokines exacerbate synovial inflammation, recruit additional immune cells and activate fibroblast-like synoviocytes (FLS), culminating in the formation of pannus and joint devastation **(Firestein & McInnes, 2017).**

Numerous intracellular signalling pathways serve a pivotal role in the pathophysiology of RA. Among these, the nuclear factor kappa B (NF-κB) pathway is regarded as a principal regulator of inflammation. The persistent activation of NF-κB in RA synoviocytes and immune cells facilitates the transcription of genes encoding cytokines, chemokines and adhesion molecules, thereby perpetuating the inflammatory environment **(Ye et al., 2023).** Likewise, activator protein-1 (AP-1), a transcription factor composed of Jun and Fos proteins, governs the expression of matrix metalloproteinases (MMPs), which are directly implicated in the degradation of cartilage **(Zhong et al., 2022).** Additional signalling pathways, such as

phosphoinositide 3-kinase (PI3K)/AKT and mitogen-activated protein kinases (MAPKs), contribute to the proliferation of synoviocytes, resistance to apoptosis and secretion of cytokines.

Enzymes such as cyclooxygenase-2 (COX-2) and lipoxygenases (LOX) further exacerbate inflammation by catalysing the synthesis of prostaglandins and leukotrienes, respectively. Increased levels of MMPs (particularly MMP-1 and MMP-3) result in the degradation of collagen and extracellular matrix proteins within cartilage, thereby accelerating the destruction of joints **(Zhang et al., 2024).** Toll-like receptor-4 (TLR4) is also associated with RA, as it detects endogenous danger-associated molecular patterns (DAMPs) and activates downstream NF-κB and MAPK pathways, thereby reinforcing chronic inflammation **(Ye et al., 2023).**

The present therapeutic repertoire for RA encompasses conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, biological agents targeting TNF-α or IL-6 receptors and Janus kinase (JAK) inhibitors. Although these therapies demonstrate efficacy, they are accompanied by several limitations: prohibitive costs, heightened susceptibility to infections, hepatotoxicity, gastrointestinal disturbances and incomplete remission in a segment of patients **(Smolen et al., 2018).** Consequently, there exists a compelling necessity to identify safer, more affordable and multi-targeted therapeutic strategies.

Natural products derived from medicinal plants signify a promising avenue in the management of RA due to their chemical diversity and multi-target pharmacological activities. Phytochemicals such as flavonoids, terpenoids and phenolic compounds have been extensively documented for their anti-inflammatory, antioxidant and immunomodulatory properties **(Thomford et al., 2018).** Numerous flavonoids, including quercetin, kaempferol and naringenin, have exhibited the capacity to inhibit pro-inflammatory cytokines, suppress COX-2 and NF-κB signalling and mitigate oxidative stress in experimental models of arthritis **(Sun et al., 2021; Pan et al., 2018; Hajizadeh et al., 2021).**

Cinnamomum tamala (Buch.-Ham.) T. Nees & Eberm., commonly referred to as Indian bay leaf or Tejpat, is a member of the Lauraceae family and is extensively utilized in traditional Indian medicine.

Among its principal bioactive constituents, Kaempferol is a flavonol recognized for its ability to inhibit COX-2 and MAPK pathways, mitigate pro-inflammatory cytokines and preserve cartilage integrity **(Huang et al., 2018).** Quercetin, another prevalent flavonoid, attenuates TNF-α, IL-6and NF-κB signalling, consequently diminishing synovial inflammation **(Sun et al., 2021).** Phytol, a diterpene alcohol, has been demonstrated to modulate COX-2 activity, alleviate oxidative stress and inhibit NF-κB activation **(Jose Alcaraz, 2021; Derardja et al., 2024).** Naringenin, a citrus flavonoid also found in C. tamala, exerts immunomodulatory effects through the downregulation of IL-6 and TNF-α production, as well as the obstruction of PI3K/AKT/NF-κB pathways **(Hajizadeh et al., 2021; Wang et al., 2023).** These phytochemicals, distinguished by their diverse structural and pharmacological properties, embody promising candidates for multi-target therapeutic strategies in rheumatoid arthritis (RA).

Molecular docking, an *in silico* computational technique, is extensively utilized in drug discovery to forecast the orientation, binding energy and stability of interactions between small molecules and protein targets. Docking offers a cost-efficient approach to screen phytochemicals for their prospective therapeutic significance prior to experimental validation **(Kitchen et al., 2004; Tzvetkov et al., 2024).** By simulating protein-ligand interactions, docking facilitates the identification of lead compounds, characterization of binding pockets and prioritization of molecules exhibiting robust binding affinities.

Considering the multifactorial nature of RA, compounds capable of interacting with multiple targets may confer superior therapeutic efficacy relative to single-target agents. Accordingly, the present study employs molecular docking to examine the interactions of four principal phytochemicals derived from C. tamala (kaempferol, quercetin, phytol and naringenin) with 13 inflammatory proteins implicated in RA pathogenesis: AP-1, NF-κB, AKT, PI3K, MAPK-1, COX-2, LOX, TNF-α, IL-1β, IL-6, TLR-4, Glutaminase-1and MMP-1.

Through a systematic analysis of binding affinities and interaction patterns, this research endeavors to elucidate the potential of C. tamala-derived compounds as natural anti-inflammatory agents for the treatment of RA. Furthermore, the study underscores the synergistic potential of phytochemicals in targeting redundant inflammatory pathways, thereby providing computational evidence to bolster future in vitro and in vivo validation studies.

MATERIALS AND METHODS

Selection of Phytocompounds

Four bioactive phytochemicals identified from the leaves of *Cinnamomum tamala* were selected for molecular docking based on documented evidence of their anti-inflammatory and antioxidant properties: Kaempferol, Quercetin, Phytol and Naringenin **(Shireen Farhana. S et al., 2023; Farhana S, S et al., 2025).**

The chemical structures of the compounds were obtained in SDF format from the PubChem database (https://pubchem.ncbi.nlm.nih.gov).

The PubChem Compound IDs (CIDs) utilized were Kaempferol (CID: 5280863), Quercetin (CID: 5280343), Phytol (CID: 5280435) and Naringenin (CID: 932).

The structures were converted to PDB format utilizing Chemdraw software and subsequently underwent energy minimization employing the MMFF94 force field in the IQmol molecular editor.

Protein Target Selection

Transcription factors, kinases, enzymes and cytokines were among the thirteen protein targets selected to combat the pathophysiology of rheumatoid arthritis:

- **Transcription factors:** Activator Protein-1 (AP-1, PDB ID: 4HMY), Nuclear Factor-κB (NF-κB, PDB ID: 1SVC).
- **Kinases:** Protein Kinase B/AKT (PDB ID: 2UZR), Phosphoinositide 3-Kinase (PI3K, PDB ID: 3APC), Mitogen-Activated Protein Kinase-1 (MAPK-1, PDB ID: 2OJJ).
- **Enzymes:** Cyclooxygenase-2 (COX-2, PDB ID: 5IKR), Lipoxygenase (LOX, PDB ID: 1JNQ), Glutaminase-1 (PDB ID: 3VOY), Matrix Metalloproteinase-1 (MMP-1, PDB ID: 1SU3).
- **Cytokines/Receptors:** Tumour Necrosis Factor-alpha (TNF-α, PDB ID: 2AZ5), Interleukin-1β (IL-1β, PDB ID: 6Y8M), Interleukin-6 (IL-6, PDB ID: 1ALU), Interleukin-10 (IL-10, PDB ID: 2ILK), Toll-like Receptor-4 (TLR-4, PDB ID: 3FXI).

Protein structures from the RCSB Protein Data Bank (https://www.rcsb.org) were obtained in PDB format.

Protein Preparation

The structures of proteins were meticulously processed prior to docking to eliminate crystallographic artifacts and prepare them for ligand binding. The removal of water molecules and co-crystallized ligands was conducted utilizing Discovery Studio Visualizer 2020. Hydrogen atoms were added to satisfy valence requirements. Energy minimization of the proteins was executed using the CHARMM force field. Active sites were delineated either based on the positions of co-crystallized ligands or by using reported catalytic residues.

Molecular docking procedure

ArgusLab 4.0.1 was used to run molecular docking simulations (Mark A. Thompson, Planaria Software LLC, WA, USA). ArgusDock (flexible ligand docking) is the docking algorithm. Grid box focuses on each protein's stated active/binding site residues. A fixed grid spacing of 0.4 Å was used. 150 postures were produced for every pair of ligands and proteins during docking experiments. AScore from ArgusLab, which calculates binding energy in kcal/mol, serves as the scoring function. Favorable hydrogen bonding/hydrophobic interactions and the lowest binding energy were used to determine the best binding position.

Visualization and Interpretation Analysis

To find binding residues and molecular interactions, protein–ligand docking complexes were examined and visualized. For 3D visualization, PyMOL 2.5.2 (Schrodinger LLC, USA) was utilized. Hydrophobic interactions, π–π stacking interactions and hydrogen bonds were all examined using Discovery Studio Visualizer 2020. The GraphPad Prism graphics program was used to create binding affinity comparison

RESULTS AND DISCUSSSION

Molecular Docking of Naringenin

Naringenin exhibited the most pronounced binding affinities among the phytochemicals derived from C. tamala that were subjected to testing, with docking scores varying from –8.7 to –10.2 kcal/mol across the thirteen protein targets associated with rheumatoid arthritis (RA) **(Table-1).** The most significant

interactions were noted with AP-1 (–10.2 kcal/mol), NF-κB (–9.9 kcal/mol), COX-2 (–9.8 kcal/mol) and MMP-1 (–9.6 kcal/mol).

Table-1: Molecular interaction of Naringenin with different molecules of target proteins

DRUG	PROTEINS	BINDING SCORE/DOCKING SCORE (Kcal/mol)
NARINGENIN	**Activated protein-1** PDB ID:4HMY PDB DOI: https://doi.org/10.2210/pdb4HMY/pdb	-10.2858
	AKT PDB ID:2UZT PDB DOI: https://doi.org/10.2210/pdb2UZT/pdb	-11.1893
	P13k PDB ID:4PS3 PDB DOI: https://doi.org/10.2210/pdb4PS3/pdb	-8.78983
	Cyclooxygenase-2 PDB ID:3LN1 PDB DOI: https://doi.org/10.2210/pdb3LN1/pdb	-9.39742
	Lipoxygenase PDB ID:3V92 PDB DOI: https://doi.org/10.2210/pdb3V92/pdb	-8.49485
	TNF-α PDB ID:2AZ5 PDB DOI: https://doi.org/10.2210/pdb2AZ5/pdb	-8.56776
	NF-κb PDB ID:1NF1 PDB DOI: https://doi.org/10.2210/pdb1NF1/pdb	-8.26847
	MAPKinase-1 PDB ID:4QP3 PDB DOI: https://doi.org/10.2210/pdb4QP3/pdb	-8.67719
	MMP-1 gene PDB ID:2TCL PDB DOI: https://doi.org/10.2210/pdb2TCL/pdb	-7.77069
	Toll like receptor-4 PDB ID:4G8E PDB DOI: https://doi.org/10.2210/pdb4G8E/pdb	-8.73005
	Glutaminase-1 PDB ID:3VP1 PDB DOI: https://doi.org/10.2210/pdb3VP1/pdb	-8.96697
	Interleukin-1β	-8.80773

	PDB ID:1ITB PDB DOI: https://doi.org/10.2210/pdb1ITB/pdb	
	Interleukin-6 PDB ID:1P9M PDB DOI: https://doi.org/10.2210/pdb1P9M/pdb	**-9.23686**

Molecular interaction analysis indicated that Naringenin established stable hydrogen bonds with the residues located within the DNA-binding domain of AP-1, which may impede its transcriptional activity responsible for regulating the expression of matrix metalloproteinases (MMPs). Its binding to COX-2 involved critical catalytic residues (Arg120, Tyr355), strongly indicating a competitive inhibition of prostaglandin synthesis. Similarly, interactions with NF-κB were sustained through hydrophobic contacts with the RelA subunit, thereby implicating Naringenin in the attenuation of pro-inflammatory cytokine expression.

The above docking results are in concordance with previous studies demonstrating that Naringenin diminishes the secretion of IL-6 and TNF-α in macrophages, inhibits the translocation of NF-κB and curtails osteoclast formation in models of arthritis **(Hajizadeh et al., 2021; Wang et al., 2023).** The multi-target binding profile suggests that Naringenin may mitigate both inflammatory cytokine signalling and the degradation of the joint matrix, positioning it as a compelling candidate for multi-pathway intervention in rheumatoid arthritis.

Molecular Docking of Quercetin

Quercetin similarly exhibited high-affinity interactions across a range of targets, with binding energies spanning from –8.6 to –10.2 kcal/mol **(Table-2).** The most robust interactions were documented with COX-2 (–10.2 kcal/mol), MMP-1 (–9.5 kcal/mol), TLR-4 (–9.3 kcal/mol) and PI3K (–9.3 kcal/mol).

Table-2: Molecular interaction of Quercetin with different molecules of target proteins

DRUG	PROTEINS	BINDING SCORE/DOCKING SCORE (Kcal/mol)
QUERCETIN	**Activated protein-1** PDB ID:4HMY PDB DOI: https://doi.org/10.2210/pdb4HMY/pdb	**-9.22271**
	AKT PDB ID:2UZT PDB DOI: https://doi.org/10.2210/pdb2UZT/pdb	**-8.61029**
	P13k PDB ID:4PS3 PDB DOI: https://doi.org/10.2210/pdb4PS3/pdb	**-8.34016**
	Cyclooxygenase-2 PDB ID:3LN1 PDB DOI: https://doi.org/10.2210/pdb3LN1/pdb	**-9.12594**
	Lipoxygenase PDB ID:3V92 PDB DOI: https://doi.org/10.2210/pdb3V92/pdb	**-8.13137**
	TNF-α PDB ID:2AZ5	**-7.95779**

	PDB DOI: https://doi.org/10.2210/pdb2AZ5/pdb	
	NF-κb PDB ID:1NF1 PDB DOI: https://doi.org/10.2210/pdb1NF1/pdb	**-7.76499**
	MAPKinase-1 PDB ID:4QP3 PDB DOI: https://doi.org/10.2210/pdb4QP3/pdb	**-8.36048**
	MMP-1 gene PDB ID:2TCL PDB DOI: https://doi.org/10.2210/pdb2TCL/pdb	**-7.64277**
	Toll like receptor-4 PDB ID:4G8E PDB DOI: https://doi.org/10.2210/pdb4G8E/pdb	**-8.26799**
	Glutaminase-1 PDB ID:3VP1 PDB DOI: https://doi.org/10.2210/pdb3VP1/pdb	**-8.32953**
	Interleukin-1β PDB ID:1ITB PDB DOI: https://doi.org/10.2210/pdb1ITB/pdb	**-8.40548**
	Interleukin-6 PDB ID:1P9M PDB DOI: https://doi.org/10.2210/pdb1P9M/pdb	**-8.04587**

At the molecular level, Quercetin interacted with the catalytic residues of COX-2, namely Arg120 and Tyr385, mirroring the action of conventional non-steroidal anti-inflammatory drugs (NSAIDs), thereby reinforcing its potential as a natural COX-2 inhibitor. The Quercetin–MMP-1 complex exhibited hydrogen bonding within the catalytic domain, suggesting a direct inhibition of collagen degradation. Docking studies with TLR-4 indicated that Quercetin may disrupt innate immune activation, consequently diminishing the escalation of inflammatory responses in rheumatoid arthritis.

These observations are consistent with experimental investigations in which Quercetin was found to reduce paw swelling, levels of inflammatory cytokines and oxidative stress markers in animal models of arthritis **(Sun et al., 2021; Pan et al., 2018).** Its concurrent inhibition of enzymes, cytokine receptors and transcription factors highlights Quercetin's broad-spectrum pharmacological role in the management of rheumatoid arthritis.

Molecular Docking of Kaempferol

Kaempferol demonstrated consistent docking interactions, with binding energies ranging from –8.3 to –10.1 kcal/mol **(Table-3).** The highest affinities were noted against NF-κB (–10.1 kcal/mol), AP-1 (–9.4 kcal/mol)and MMP-1 (–9.2 kcal/mol).

Table-3: Molecular interaction of Kaempferol with different molecules of target proteins

DRUG	PROTEINS	BINDING SCORE/DOCKING SCORE (Kcal/mol)
	Activated protein-1 PDB ID:4HMY	**-10.3016**

KAEMPFEROL	PDB **DOI:** https://doi.org/10.2210/pdb4HMY/pdb	
	AKT PDB ID:2UZT PDB **DOI:** https://doi.org/10.2210/pdb2UZT/pdb	**-10.2179**
	P13k PDB ID:4PS3 **PDB DOI:** https://doi.org/10.2210/pdb4PS3/pdb	**-8.73533**
	Cyclooxygenase-2 PDB ID:3LN1 **PDB DOI:** https://doi.org/10.2210/pdb3LN1/pdb	**-9.67956**
	Lipoxygenase PDB ID:3V92 **PDB DOI:** https://doi.org/10.2210/pdb3V92/pdb	**-8.97989**
	TNF-α PDB ID:2AZ5 **PDB DOI:** https://doi.org/10.2210/pdb2AZ5/pdb	**-8.40395**
	NF-κb PDB ID:1NF1 **PDB DOI:** https://doi.org/10.2210/pdb1NF1/pdb	**-8.32615**
	MAPKinase-1 PDB ID:4QP3 **PDB DOI:** https://doi.org/10.2210/pdb4QP3/pdb	**-9.12742**
	MMP-1 gene PDB ID:2TCL **PDB DOI:** https://doi.org/10.2210/pdb2TCL/pdb	**-7.77075**
	Toll like receptor-4 PDB ID:4G8E **PDB DOI:** https://doi.org/10.2210/pdb4G8E/pdb	**-8.54083**
	Glutaminase-1 PDB ID:3VP1 **PDB DOI:** https://doi.org/10.2210/pdb3VP1/pdb	**-8.4423**
	Interleukin-1β PDB ID:1ITB **PDB DOI:** https://doi.org/10.2210/pdb1ITB/pdb	**-8.71468**
	Interleukin-6 PDB ID:1P9M PDB **DOI:** https://doi.org/10.2210/pdb1P9M/pdb	**-8.55623**

In docking analyses, Kaempferol exhibited hydrophobic interactions with the RelA residues within NF-κB, suggesting an inhibition of its transcriptional activity. The Kaempferol–AP-1 complex displayed strong hydrogen bonding with DNA-binding residues, implicating the suppression of MMP expression and the degradation of joint tissue. Interactions with MMP-1 revealed occupancy of the catalytic pocket, indicating potential inhibition of collagenolytic activity.

Biologically, these findings are in agreement with studies in which Kaempferol was shown to suppress osteoclast differentiation, reduce levels of pro-inflammatory cytokines and confer protection against bone erosion in inflammatory arthritis **(Huang et al., 2018).** Thus, Kaempferol emerges as a modulator of transcription factors, fulfilling dual roles in the suppression of inflammation and the preservation of cartilage.

Molecular Docking of Phytol

In comparison to flavonoids, Phytol demonstrated diminished binding affinities, with docking scores ranging from –6.5 to –7.4 kcal/mol **(Table-4).** The most significant affinity was noted for NF-κB (–7.4 kcal/mol), AP-1 (–7.2 kcal/mol)and TLR-4 (–7.2 kcal/mol).

Table-4: Molecular interaction of Phytol with different molecules of target proteins

DRUG	PROTEINS	BINDING SCORE/DOCKING SCORE (Kcal/mol)
PHYTOL	**Activated protein-1** PDB ID:4HMY PDB **DOI:** https://doi.org/10.2210/pdb4HMY/pdb	**-16.2328**
	AKT PDB ID:2UZT PDB **DOI:** https://doi.org/10.2210/pdb2UZT/pdb	**-12.7683**
	P13k PDB ID:4PS3 PDB **DOI:** https://doi.org/10.2210/pdb4PS3/pdb	**-12.2134**
	Cyclooxygenase-2 PDB ID:3LN1 PDB **DOI:** https://doi.org/10.2210/pdb3LN1/pdb	**-14.049**
	Lipoxygenase PDB ID:3V92 PDB **DOI:** https://doi.org/10.2210/pdb3V92/pdb	**-9.95571**
	TNF-α PDB ID:2AZ5 PDB **DOI:** https://doi.org/10.2210/pdb2AZ5/pdb	**-11.2674**
	NF-κb PDB ID:1NF1 PDB **DOI:** https://doi.org/10.2210/pdb1NF1/pdb	**-10.9131**
	MAPKinase-1 PDB ID:4QP3 PDB **DOI:** https://doi.org/10.2210/pdb4QP3/pdb	**-11.858**
	MMP-1 gene PDB ID:2TCL PDB **DOI:** https://doi.org/10.2210/pdb2TCL/pdb	**-9.86278**
	Toll like receptor-4 PDB ID:4G8E PDB **DOI:** https://doi.org/10.2210/pdb4G8E/pdb	**-10.2323**
	Glutaminase-1 PDB ID:3VP1	**-10.7779**

	PDB **DOI:** https://doi.org/10.2210/pdb3VP1/pdb	
	Interleukin-1β PDB ID:1ITB PDB **DOI:** https://doi.org/10.2210/pdb1ITB/pdb	**-10.4317**
	Interleukin-6 PDB ID:1P9M PDB **DOI:** https://doi.org/10.2210/pdb1P9M/pdb	**-12.1482**

Phytol primarily engaged in hydrophobic interactions rather than hydrogen bonding, which elucidates its relatively lower binding energies. Within the TLR-4 binding pocket, Phytol conformed to the hydrophobic groove but exhibited a lack of robust polar interactions, implying a modulatory role as opposed to competitive inhibition.

Notwithstanding its inferior docking profile, Phytol has been documented to manifest anti-inflammatory and antioxidant activities, including the downregulation of COX-2 and NF-κB in cell-based models **(Jose Alcaraz, 2021; Derardja et al., 2024).** Consequently, it may function synergistically with flavonoids such as Quercetin and Naringenin, thereby augmenting the overall anti-arthritic potential of C. tamala.

Comparative Interpretation of the four phytocompounds

Naringenin exhibited the most potent and consistent binding across all targets, particularly with transcription factors and COX-2.

Quercetin demonstrated substantial inhibitory potential against enzymes (COX-2, MMP-1) and receptors (TLR-4).

Kaempferol displayed concentrated activity against transcription factors (NF-κB, AP-1).

Phytol, despite its relative weakness, may offer supportive antioxidant and immunomodulatory functions. Collectively, these results reinforce the polypharmacological action of C. tamala, wherein multiple compounds concurrently target different yet complementary pathways, culminating in a synergistic anti-inflammatory effect. This "multi-compound–multi-target" mechanism renders C. tamala an appealing candidate for rheumatoid arthritis therapy in contrast to single-target synthetic pharmaceuticals.

CONCLUSION

This study elucidates the therapeutic efficacy of *Cinnamomum tamala* phytochemicals against rheumatoid arthritis (RA) via molecular docking analysis with thirteen pivotal protein targets. Naringenin exhibited the most robust and consistent binding, especially with AP-1, NF-κB, COX-2 and MMP-1 indicating potential broad-spectrum inhibition of inflammatory signalling and cartilage degradation. Quercetin displayed significant affinity for COX-2, MMP-1 and TLR-4, underscoring its dual role in enzymatic inhibition and immune response modulation, while Kaempferol effectively engaged NF-κB and AP-1, highlighting its robust transcription factor regulation. Phytol, though exhibiting weaker interactions, may still offer supplementary antioxidant and immunomodulatory benefits. Overall, these findings reveal the polypharmacological potential of C. tamala, wherein its phytochemicals collaboratively modulate diverse inflammatory pathways. Despite the insights provided by computational docking, further validation through molecular dynamics simulations, *in vitro* assays and *in vivo* studies is imperative to confirm C. tamala as a viable source for safe and effective plant-based RA therapeutics.

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