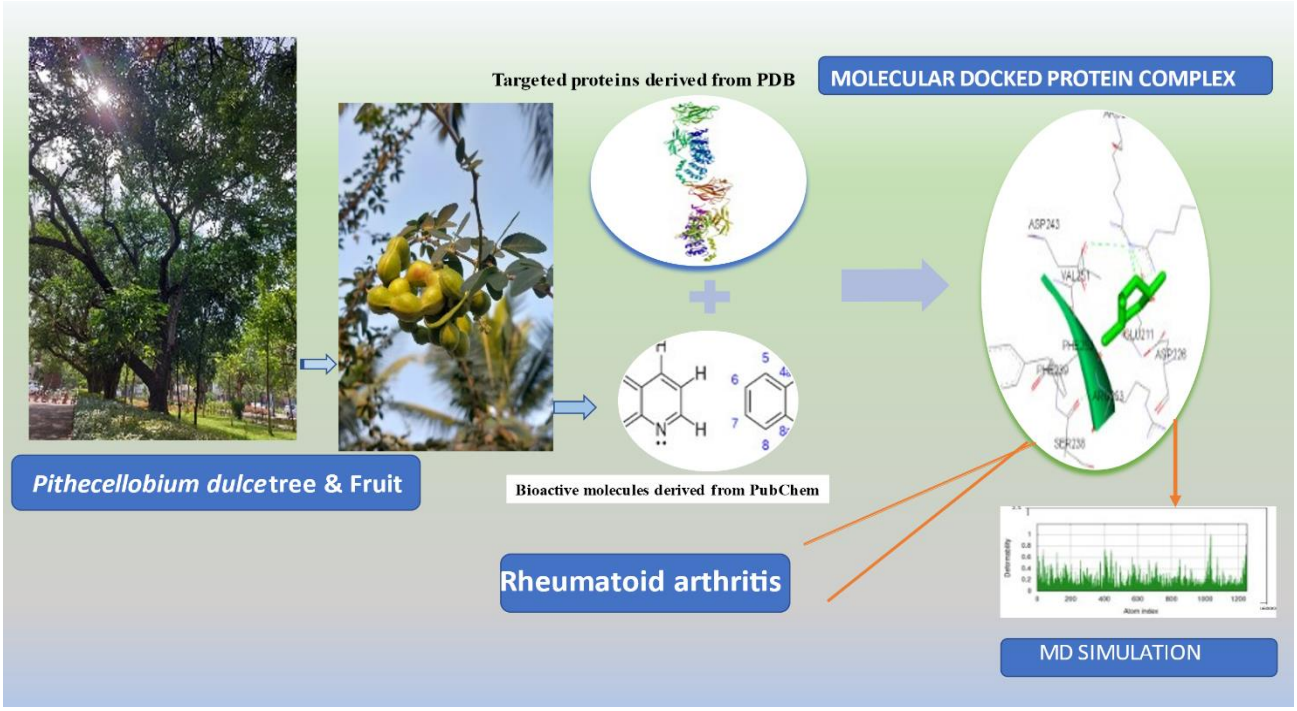
In silico Analysis of Bioactive Compounds from *Pithecellobium dulce:* A Promising Approach for Targeting Proteins in Rheumatoid Arthritis

Dongre Nilima[1], Tungal Soumya[1]* and Parvatikar Prachi[2]
1. Department of Biochemistry, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to Be University), Vijayapur-586103, Karnataka, INDIA
2. Science and Technology, BLDE (Deemed to Be University), Vijayapur-586103, Karnataka, INDIA
*soumyatungal123@gmail.com

Abstract:
Rheumatoid Arthritis (RA) is a chronic autoimmune disorder that causes joint and bone destruction, severe pain, stiffness and disability, decreasing the quality of life for those affected. The study evaluated Pithecellobium dulce as a potential RA treatment using in silico analysis. Pithecellobium dulce's key bioactive components were tested for their ability to suppress rheumatoid arthritis (RA). Molecular binding experiments were carried out, evaluating their interactions with the new RA target proteins IkBα and MMP1, as well as their drug-likeness and toxicity. To investigate the efficacy and safety of bioactive compounds in the treatment of RA, molecular dynamics (MD) simulations were performed using IMOD software. The selected compounds, assessed through ADMET analysis, exhibited favourable drug-like properties like low toxicity. Additionally, molecular docking demonstrated strong binding energy with the target proteins. Further, MD simulations confirmed the stability and efficacy of the compound-protein complexes. These findings suggest that the bioactive compounds have potential therapeutic value. However, further in vivo and in vitro studies are necessary to determine its effectiveness and to validate its pharmacological activity conclusively.

Keywords: Rheumatoid arthritis, Bioactive compounds, *Pithecellobium dulce*, IkBα, MMP1, H- DOCK.



Graphical Abstract

Rheumatoid Arthritis (RA) is a chronic inflammatory condition that destroys joints and bones, lowering people's quality of life. As a result, there is a critical need for more effective and safer treatments. Natural therapy has the potential to treat RA more effectively, with less toxicity and fewer side effects. *In silico* analysis was used in a study to examine *Pithecellobium dulce* as a potential therapy for rheumatoid arthritis. Two of the eight bioactive compounds demonstrated high binding energy with target proteins indicating potential therapeutic efficacy. However, additional *in vivo* and *in vitro* investigations are required to demonstrate its efficacy and to validate its pharmacological action. Natural medicine may provide safer, more effective treatments for RA.

Introduction

Around 1% of the world's population suffers from rheumatoid arthritis (RA), a chronic inflammatory condition.[27] This autoimmune condition causes painful and uncomfortable symptoms such as joint swelling, stiffness and pain in the hands, wrists, knees and feet. These symptoms significantly impact the individual's quality of life. The pathogenesis of rheumatoid arthritis (RA) involves communication between immune cells and those in the joint.[9] Among these, fibroblast-like synoviocytes (FLS) play a crucial role. FLS are cells of mesenchymal origin that make up the intimal layer of the synovium and regulate local homeostasis while overseeing proper joint functioning. **[14]** The NF-kB signalling system, which includes RelA (p65), c-Rel, RelB, NF-kB1 (p50) and NF-kB2 (p52), is critical for inflammatory development.

Initially, inhibitory proteins like IkBα keep these factors in the cytoplasm and prevent NF-kB activation. Dysregulated IkBα function in RA causes continual NF-kB activation, leading to inflammation and joint degeneration. When stimulated by pro-inflammatory signals, IkBα degrades, allowing active NF-kB to reach the nucleus and drive gene transcription. In addition, MMP1, a matrix metalloproteinase, remodels the extracellular matrix in RA, contributing to tissue damage. Increased MMP1 activity accelerates joint cartilage breakdown and bone erosion, exacerbating the inflammatory response in RA.[3]

Understanding the functions of IKBα and MMP1 in RA offers an understanding of the dysregulated immune responses, ongoing inflammation and tissue destruction seen in RA**.[19]** By exploring new, innovative natural bioactive compounds, there is a potential to effectively reduce inflammation and facilitate remodelling processes associated with these proteins. Most commonly used modern medications like DMARDs for treating RA have side effects like nausea, vomiting and weakness, depending upon the drug type used. Thus, looking for alternative medicines with fewer or no side effects is necessary.

Natural bioactive phytochemicals have become popular treatment options for various inflammatory diseases.[1,19] *Pithecellobium dulce*, generally known as Manila tamarind, is a small to medium-sized, spiny, evergreen tree that grows over the Indian plains. *Pithecellobium dulce* fruit is edible and has many calories, protein, fat and carbohydrates.[23] The present study aims to investigate potential active compounds. It is necessary to explore the new drug design to target particular drugs with a 3-D design using different bioinformatics tools and techniques. The study predicts the drug potential and design of the structure of the drug with their atom's interaction and toxicity properties by *in silico* approach.

Material and Methods

Retrieval of the target protein: The 3-D crystal structure of the target proteins IkBα and MMP1 was obtained from the Protein Data Bank. The PDB IDs (https://www.rcsb.org/) were used respectively. The protein structures were then imported into Accelrys Discovery Studio for further analysis. Water molecules, ions, other non-receptor atoms and other substances were eliminated from the systems. The resulting protein structures were then prepared for docking studies.[8,12]

Physicochemical ADME/T properties: The selected active compounds were evaluated based on physicochemical parameters including molecular weight (<500), H-bond donor (HBD), H-bond acceptor (HBA), total number of rotatable bonds (<10), total polar surface area (<140) and atomic molar refractivity (42-130). These qualities are critical for understanding drug's interaction with biological targets, solubility and capacity to cross cell membranes. The SWISS ADMET tool was used to evaluate these characteristics. This tool uses computational methods to estimate a molecule's physicochemical qualities based on its structure. Furthermore, the technique predicts key ADMET characteristics such as human oral availability and brain/blood barrier permeability. BBB permeability is very significant since it impacts a drug's capacity to pass through the blood-brain barrier and reach its target in the brain.**[8]**

Molecular interaction Studies: Crystal structures of IkBα and MMP1 were obtained from the Protein Data Bank. Any undesirable ligands, linkages, or water molecules were eliminated from the 3D structures of the proteins using Discovery Studio. Ligands such as quinoline, nootkatone, 2,5,6 trimethyl 1,3 oxathiane, trans three methyl's 2N propyl thiophane, tetraneurin-f, ethyl two bromo four methyl's, six dimethyl silibenzophane and 2propyl tetrahydropyran 3-cool were retrieved from the PubChem Database in SDF format.

The selected ligands were docked against the IkBα protein using the HDOCK server (http://hdock.phys.hust.edu.cn).[12] This service provides a complete approach to macromolecular docking, template-based modelling, structure prediction and homology search. It takes both sequences and structures as input and uses intrinsic scoring systems to predict protein-ligand docking. HDOCK uses the following scoring functions:

Molecular Dynamic Simulation studies: This work used molecular dynamics (MD) simulations, a computational tool for evaluating atomic and molecule movement across time, to obtain insight into biological systems' dynamic properties. The iMod server (iMODS) aided these simulations by providing enhanced normal mode analysis (NMA) and a user-friendly interface for exploring potential paths engaging with created objects in 3D. Docking simulations used root mean square deviation (RMSD) to measure structural stability, ligand-protein interactions and binding energies.[22] Overall, MD simulations with iMod facilitated the analysis of dynamic behaviour and binding interactions in ligand-protein complexes, providing valuable insights into structural dynamics and functional consequences

Results

Screening of ligands from database and literature: *Pithecellobium dulce* ligands were screened from the literature and eight were further chosen. Due to their excellent nutritional value and medicinal potential, *P. dulce's* fruits have attracted much interest. Numerous pharmacological activities of *P. dulce's* fruit extract includes anti-diabetic, antioxidant, gastroprotective, anti-inflammatory, hepatoprotective, cardioprotective, anti-bacterial and H+/K+ ATPase inhibitory effects.

The human IKBα protein: IKBα, a protein having 317 amino acids and a molecular weight of 140.6 kDa, was structurally characterised using X-ray crystallography at 2.8 Å resolution. The crystallographic study revealed two chains within the asymmetric unit: chain A (IKB alpha) and chain B (p50 subunit of NF-kappa B). IKBα's ankyrin repeat domain inhibits NF-kappa B-mediated gene transcription via interacting with the p50 subunit's DNA-binding region.

Matrix metalloproteinase-1 (MMP1): MMP1, which has a molecular weight of 85.04 kDa, was structurally characterised using X-ray crystallography at a resolution of 2.15 Å. The asymmetric unit contains chains A (MMP1) and B (Zn^{2+} ion), with one zinc ion attached to MMP1's active site. MMP1 has a catalytic domain and a hemopexin-like domain. The catalytic domain is a tight globular fold with β-sheets and α-helices whereas the hemopexin-like domain has β-sheets and a short α-helix. MMP1's active site contains a zinc ion, three histidine residues and a water molecule. Furthermore, the catalytic domain has a conserved Met-Tyr-Gly-Cys-Thr-Pro-Cys sequence motif, essential for MMP1's enzymatic activity.

Table 1
PubChem details selected bioactive compounds from *P. dulce*

S.N.	Compound name	PubChem id	Molecular weight (g/mol)	Molecular formula
1	Quinoline	7047	129.16	C_9H_7N
2	Nootkatone	1268142	218.33	$C_{15}H_{22}O$
3	2,5,6-Trimethyl1,3 oxathiane	548225	146.25	$C_7H_{14}OS$
4	Trans three methyl, 2N-propylthiophane	6429953	140.25	$C_8H_{12}S$
5	Tetraneurin-f	01306773	366.4	$C_{19}H_{26}O_7$
6	Ethyl 2-bromo-4-methyl-6-dimethylsilylbenzothiophe 5-carboxylate	2824057	250.12	$C_7H_8BrNO_2S$
7	2-Propyltetrahydropyran-3-ol.	541755	144.21	$C_8H_{16}O_2$
8	Quercetin	5280343	302.23	$C_{15}H_{10}O_7$

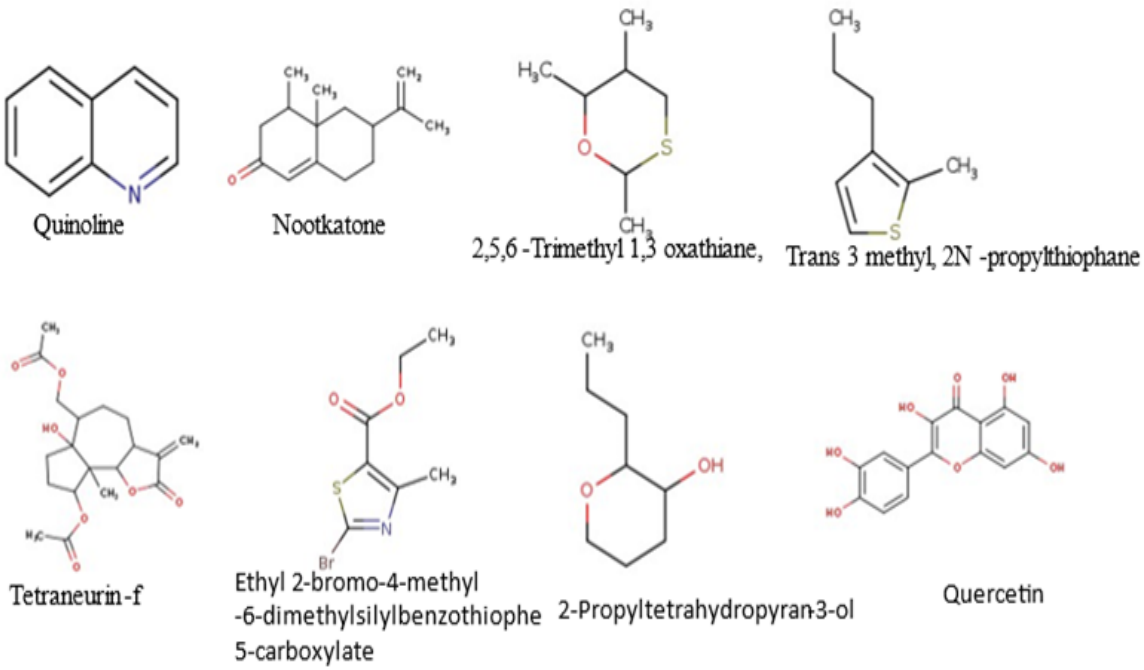


Figure 1: Chemical structure of selected 7 molecules by PubChem

Table 2
Selected targeted proteins

S.N.	Name of the Proteins	PDBID	Class	Molecular weight (g/mol)
1	IKBα	1NFI	Homo sapiens	140.6 kDa
2	MMP1	2CLT	Homo sapiens	85.04kDa

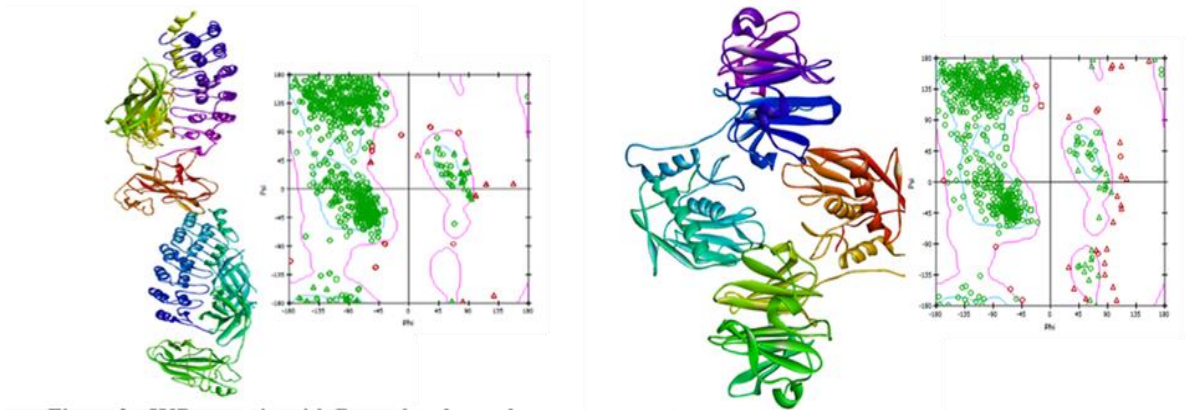


Figure 2: IkBα protein with Ramachandran plot and MMP1 protein with Ramachandran plot
The Ramachandran plot: Shows energetically allowed regions for backbone angles in protein structure, indicating favorable or unfavorable confirmations. It helps to evaluate protein structure quality and identify errors. Favored regions are energetically stable (green), while disallowed regions are unfavorable (red)

Table 3
DME/T analysis of the selected compounds

Name of the Compounds	No. H-bond acceptors	No. H-bond donor	TPSA <140	Class	GI absorption	BBB permeant	Lipinski rule	Violation
Quinoline	1	1	12.89 Å²	Soluble	High	Yes	Yes	0
Nootkatone	1	1	17.07 Å²	Soluble	High	Yes	Yes	0
2,5,6-Trimethyl1,3 oxathiane	1	1	34.53 Å²	Soluble	High	Yes	Yes	1
Trans three methyl, 2N-propylthiophane	0	0	28.24 Å²	Soluble	High	Yes	Yes	0
Tetraneurin-f	7	7	99.13 Å²	Soluble	High	No	Yes	0
Ethyl 2-Bromo -4-methyl-6-dimethylsilylbenzothiophe 5-carboxylate	3	3	67.43 Å²	Soluble	High	Yes	Yes	0
2-Propyltetrahydropyran-3-ol.	2	2	29.46 Å²	Very soluble	High	Yes	Yes	0
Quercetin	7	5	131.36 Å²	Soluble	High	No	Yes	0

Screening of ADME/T properties by SWISS ADMET online tool: The SWISS ADMET tool revealed that the drug candidates had favourable absorption and distribution qualities which complied with Lipinski's rule, a significant determinant in their efficacy. However, medications that did not follow this guideline were rejected due to possible solubility and permeability concerns. A selection of the remaining candidates underwent additional docking research to find favourable ligand-protein interactions. These data emphasise the need for further optimisation to improve the ADME/T characteristics of these medication candidates.

Molecular interaction studies: This work used molecular docking to analyse the binding and energy of chosen ligands with target proteins IKBα and MMP1. The top protein-ligand complexes were found based on intrinsic scoring functions. All selected ligands showed promising activity with IKBα and MMP1 having the highest affinity at the

active binding site. The binding energy of selected ligands was estimated using the Discovery Studio Visualizer tool and receptor-ligand interactions were further analysed to identify their 2D structure. The study identifies binding locations on IKBα and MMP1 surfaces that promote stable complex formation through Van der Waals interactions and conventional bonds. These data suggest that these ligands have potential for treating RA, but more research is needed.

Molecular dynamics simulation: The iMod server used molecular dynamics simulations and normal mode analysis to evaluate protein and ligand movements in docked complexes including quinoline, quercetin, IkBα and MMP1. Peaks on the main-chain deformability graph indicated extremely malleable regions, with atomic index 1000 having the highest peak at a deformability value of one.

iMod determined the B-factor values which indicate protein structural flexibility and temperature fluctuations. Higher B-factor values suggest more atomic mobility and conformational changes whereas lower values imply inflexible regions with minimal mobility which helps to identify functionally significant portions within the docked complex.

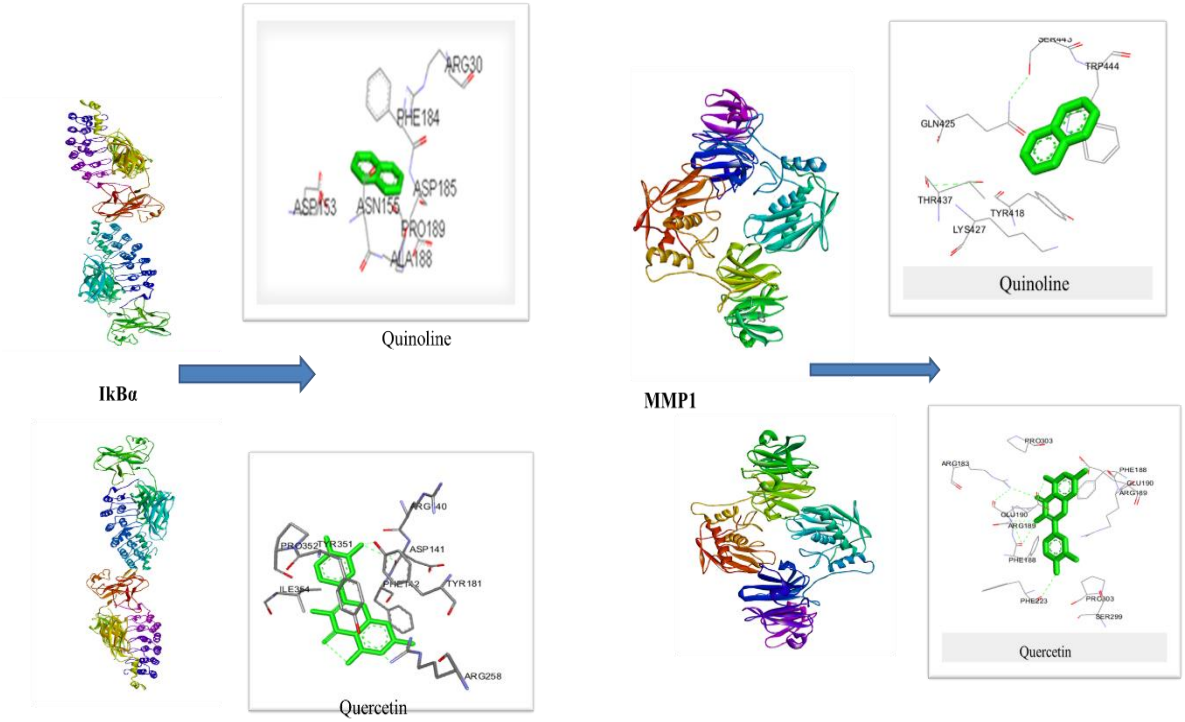


Figure 3: Structure in three dimensions with PBD ID (IkBα and MMP1), molecular interaction with quinoline and quercetin by H-dock server

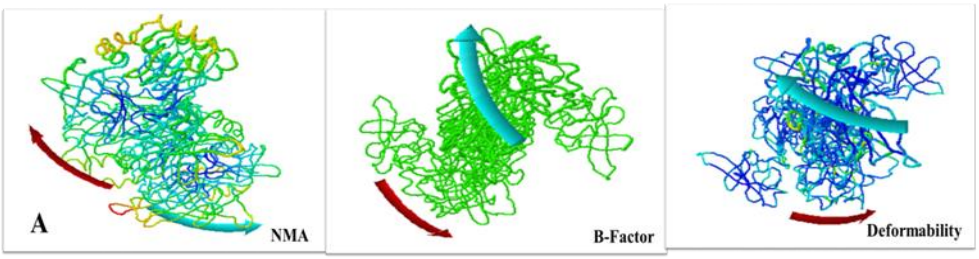
Table 4
Docking score of each of the compounds with IkBα and MMP1 protein

S.N.	Name of the compounds	IKBα			MMP1		
		Binding energy (kcal/mol)	Confidence Score	Ligand Rmsd A^0	Binding energy (kcal/mol)	Confidence Score	Ligand Rmsd A^0
1	Quinoline	-68.23	0.163	149	-84.38	0.212	82.68
2	Nootkatone	-79.97	0.197	100	-81.71	0.203	53.94
3	2,5,6-Trimethyl1,3 oxathiane	-57.33	0.135	118.74	-64.63	0.153	62.69
4	Trans 3 methyl, 2N-propylthiophane	-90.62	0.23	148.64	-108.42	0.303	67.59
5	Tetraneurin-f	-91.72	0.237	99.00	-95.3	0.251	54.76
6	Ethyl 2-bromo-4-methyl-6-dimethylsilylbenzothiophe 5-carboxylate	-64.45	0.153	65.76	-61.7	0.146	55.01
7	2-Propyltetrahydropyran-3-ol	-149.02	0.49	142.64	-136.4	0.43	54.84
8	Quercetin	-154.26	0.52	62.01	-152	0.511	53.11

Eigen values produced from iMod indicate vibrational frequencies associated with collective atom motions which provide information about system dynamics, flexibility and structural changes. Lower Eigen values indicate slower global motions, but higher Eigen values suggest faster localised vibrations. The covariance map in iMod displays a value matrix, with each element representing the covariance between pairs of atoms. The values are commonly represented by the covariance matrix specifies whether two residues are correlated (red), uncorrelated (white), or anti-correlated (blue).

iMod simulations using quinoline and quercetin docking indicate MMP1 protein flexibility, particularly at the hinge. B-factor values reflect adaptability: lower values imply rigidity while higher values indicate increased mobility and structural changes. The B-factor graph helps comprehend docked complexes by demonstrating atom flexibility. Eigen values from iMod show MMP1 dynamics and structure-function relationships with higher values indicating faster vibrations and lower values indicating slower motions.

The covariance map in iMod depicts atomic pair interactions in MMP1. Correlations are represented by red, no correlations by white and anticorrelations by blue. It indicates regions with correlated or anti-correlated movements, which are most likely relevant to protein activity. This map improves our understanding of MMP1 dynamics and structure-function relationships.



Molecular mobility evaluated by NMA of the docked complexes: IkBα with A) Quinoline,

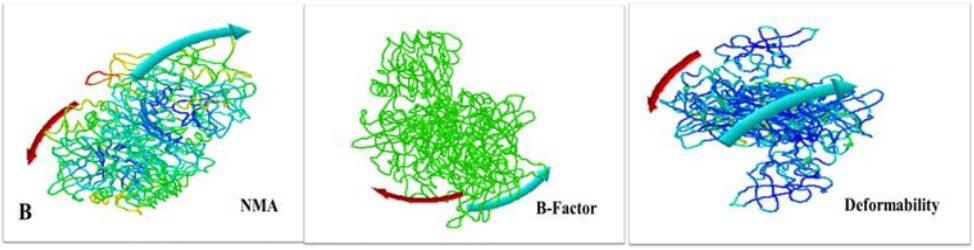


Figure 4: Molecular mobility evaluated by NMA of the docked complexes: IkBα with B) Quercetin

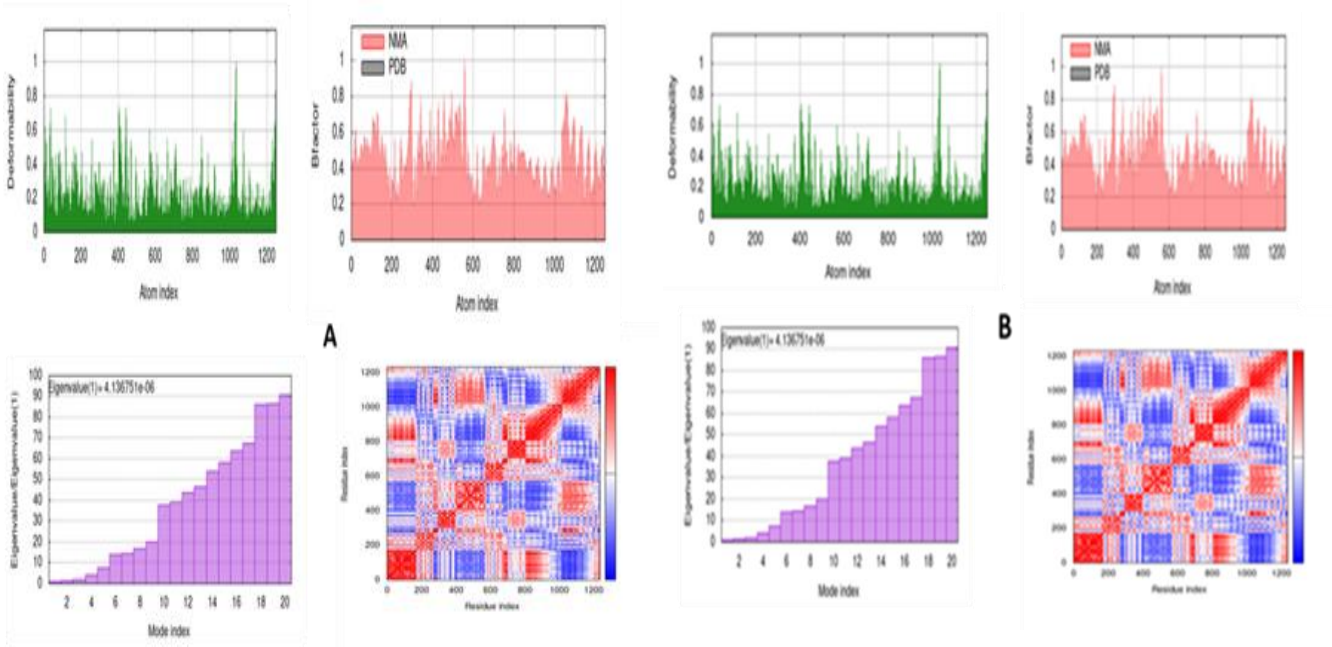


Figure 5: Outputs of Molecular dynamic simulation in iMODS for IkBα with (A) Quinoline and (B) Quercetin deformability factor plot, Eigen value, Variance plot and Covariance plot

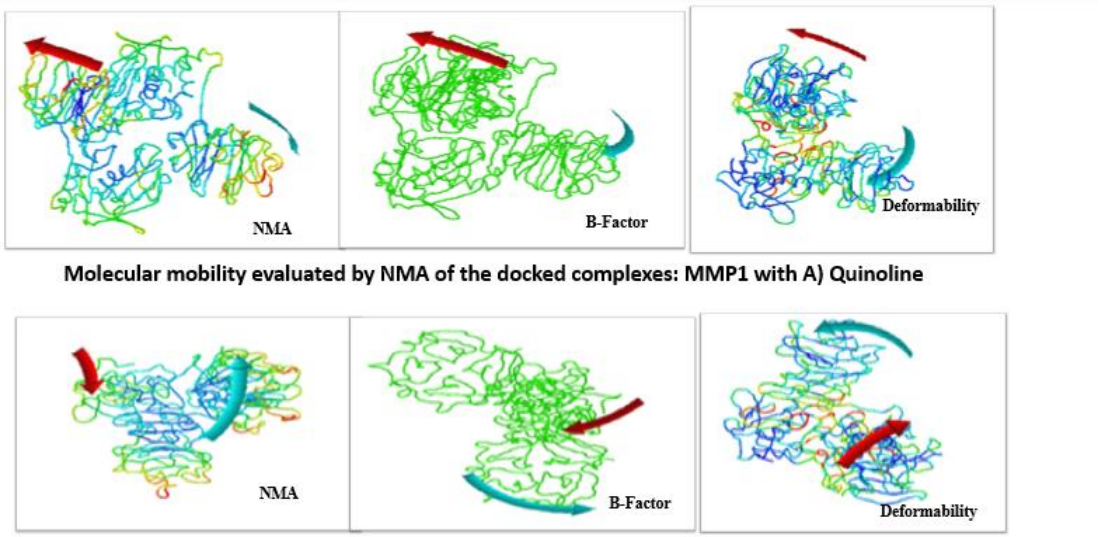


Figure 6: Molecular mobility evaluated by NMA of the docked compexes: MMP1 with Quercetin

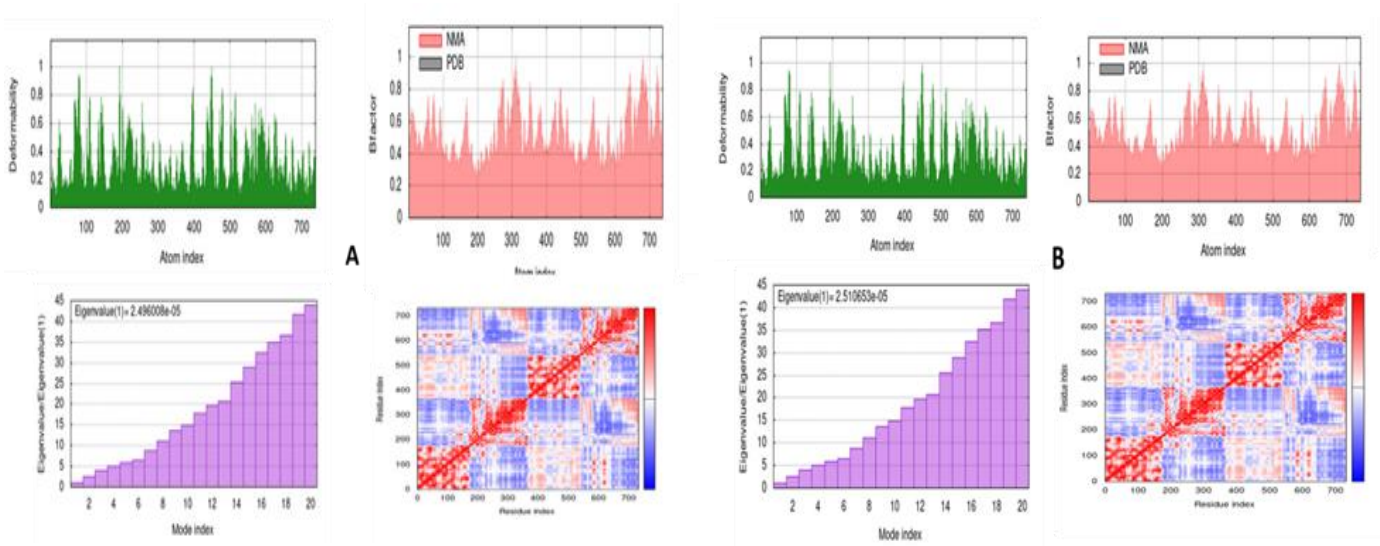


Figure 7: Outputs of molecular dynamics simulations in iMODS for MMP1 with (A) Quinoline and (B) Quercetin: deformability-factor plot, Eigen value and Variance plot and Covariance map

Discussion

Millions of people throughout the world suffer with rheumatoid arthritis (RA), a chronic autoimmune illness. Constant inflammation is one of its defining features and various symptoms that significantly diminish the quality of life for those affected.[27] The development of RA is believed to be influenced by various factors including genetic, epigenetic, environmental, metabolic, immunological and microbial factors.[13] The interaction between various immune cells also plays a role in the development of RA, with different behaviour depending on the specific disease context and microenvironment.

Biological DMARDs target extracellular factors to successfully treat RA inflammation whereas NSAIDs only provide brief pain relief. As a result, over 60% of RA patients seek alternative herbal therapies for long-term treatment.[15]The hunt for natural bioactive compounds with few side effects has escalated as a result of the health hazards associated with inflammation and the growing interest in natural alternatives to synthetic medications. These compounds should promote leukocyte recruitment, improve microvascular function, raise vascular permeability and decrease the release of pro-inflammatory cytokines.[23]

Inflammation sets off a series of biochemical reactions involving adjacent blood arteries, the immune system and numerous cells in the damaged tissue. Chronic inflammation occurs when inflammation persists, causing persistent changes in tissue composition characterised by a cycle of tissue damage and repair. Experimental procedures are employed.[16] Our research aimed to uncover useful nutraceuticals from the *Pithecellobium dulce* plant that could successfully cure arthritis while posing minimal biological hazards. We used *in silico* drug discovery, which makes use of existing drug databases, to find new medications for conditions such as arthritis. Molecular docking investigation found that IkBα and MMP1 proteins have a significant role

in lowering RA inflammation, highlighting the potential of natural medicines in controlling inflammation-related illnesses. More *in vivo* and *in vitro* researches are required to confirm the efficacy of these compounds.

Conclusion

Our findings suggest that quinoline and quercetin are attractive chemicals for producing anti-inflammatory supplements. Their nutritional and pharmacological qualities make them ideal candidates for therapeutic intervention in a variety of disorders. Molecular docking study indicates a considerable affinity for targeted proteins, specifically IkBα and MMP1, which are important in the pathogenesis of inflammatory disorders. Furthermore, ADME/T study showed low toxicity, ensuring safety for rheumatoid arthritis supplements. However, more in vivo and *in vitro* researches are required to completely evaluate their usefulness. Our findings help to better understand the therapeutic potential of quinoline and quercetin from *Pithocellobium dulce* and establish the framework for future research in this area.

Acknowledgement

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