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COMPUTATIONAL INSIGHTS INTO THE BINDING EFFICIENCY OF PHYTOCOMPOUNDS IN ERANDADI KWATHAM: A MOLECULAR DOCKING APPROACH

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Keywords:

Rheumatoid arthritis, TNF-α, HK-II, Polyherbal formulation, Molecular Docking, Ayurinformatics

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ABSTRACT: Rheumatoid arthritis (RA) is a chronic inflammation disorder that primarily affects the joints and leads to the progressive destruction of joints, synovial hyperplasia bone, and cartilage degeneration. Globally 1% of the world population was affected by rheumatoid arthritis. The present study focused to identify the bioactive phytocompounds of polyherbal formulation-Erandadi Kwatham and to determine its potential in inhibiting the targets TNF-α and Hk-II, which are associated with rheumatoid arthritis. The 3D structure of the phytocompounds were retrieved and analyzed for its physicochemical properties, toxicity, and drug-likeness were determined using the Qikprop module in maestro Schrodinger software. Among, only six compounds satisfied the ADME properties and followed drug-likeness. Further the phytocompounds triethyl citrate (6506), butanedioic acid, hydroxyl diethyl ester (24197), L-Valine, ethyl ester (87182), phenylacetic acid (97942), 7-trihydroxy-1-methyl – 8 - methylene-1, 4a-lactone-10-methyl (539615), and pectolinarigenin (5320438), were analyzed using molecular docking studies against the protein targets, TNF-α and Hk-II. The compounds triethyl citrate and pectolinarigenin were observed with significant binding efficiency of -3.47 and -5.88 kcal/mol against the respective targets TNF-α (2az5) and Hk-II (2nzt). In conclusion, the reported compounds could be further considered for molecular dynamics to evaluate its stability and respective experimental analysis, therefore to be considered as an effective alternative for treating rheumatoid arthritis.

INTRODUCTION: Rheumatoid arthritis is an inflammatory autoimmune disorder that affects the synovial joint tissues, leads to the degeneration of bone and cartilage [1]. It impacts 1% of the global population [2].

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Its origin, evolution and pathogenesis remains unclear, where scientific report evidences various environmental, genetic and epigenetic factors has a crucial role in the development of RA[3].

The current treatment options of the RA includes non-steroidal anti-inflammatory drugs (NSAIDS), diseases modifying anti-rhematic drugs (DMARDS), corticoids, glucocorticoids, conventional as well as traditional synthetic and biological DMARDS. The treatment objective focuses on mitigating the inflammation in the

affected joints and alleviating the pain. The primary goal of the treatments is to reduce the risk, disease management and increase the lifespan of the individual's affected with the RA. In several cases, extended treatments of NSAIDS, DMARDS are associated with the spectrum of adverse effects that includes hepatotoxicity, cardiovascular issues, gastrointestinal ulcer, etc. Moreover the conventional treatments are expensive [4, 5].

Tumor Necrosis Factor (TNF)-α is a predominant inflammatory cytokine found in most of the arthritis patients [6], that stimulates the synthesis of collagenase in synovial fibroblast and chondrocytes of the articular cartilage. These conditions lead to joint cartilage damage, synovial hyperplasia, and bone erosion [7], further activates the receptors like TNFR1 and TNFR2 through the consecutive inflammatory responses such as apoptosis, differentiation, proliferation, and cell migration [8]. As a result, TNF- α targeting therapeutics has been considered in a few decades as an effective treatment and is also evident for its success in treating various inflammatory diseases [9]. Hexokinase (HK) is an enzyme that involved in the first step of glycolysis pathway to convert glucose into glucose-6 phosphate. Hexokinases were found in four isoforms (Hexokinase-I, -II, -III and -IV), where hexokinase-I & -II were highly expressed in RA patients. In general, hexokinase maintains the concentration gradient of glucose within the cell and regulates the glucose utilization. The elevation of the HK-II increases the secretion of proinflammatory cytokines which exacerbates the inflammatory response [10, 11].

Henceforth, the present study targets the HK-II which could be the effective therapeutic target. Ayurveda, the Indian traditional systems of medicine uses polyherbal formulations with specific ingredients as a treatment for many disease conditions. Erandadikwatham is mentioned in Bhaishajya Rathnavali. The ingredients of the Erandadikwatham include Erandam (*Ricinus Communis*), Gokshuram (*Tribulus Terrestris),* Rasna (*Alphinia galanga*), Satapushpa (*Anethum Graveolens*), Punarnava (*Boerhavia diffusa*). The formulation has effective anti-inflammatory and anti-oxidant property that has been used as ayurvedic medications for RA. In this concern, the present study focuses on identifying the effective phytocompounds from Erandadikwatham. *Alpinia galanga* belongs to the family of Zingiberaceae. It is commonly known as Rasna Greater Galangal or Kulinja. It has various pharmacological properties such as anti-rheumatism, anti-hypertension, anti-inflammatory, antioxidant, anticancer, antiviral, antimicrobial and effective in treating bronchitis, chronic enteritis and microbial infections [11].

Tribulus terrestris L. belongs to the Zygophyllaceae family is widely used to treat inflammation, heart, blood vessel-related ailments, microbial infections, oxidative damage, hormonal problems, and help to repair muscles [12]. *Ricinus communis* belongs to Euphorbiaceae and is known as the caster oil plant which has the properties of anti-oxidant, antibacterial, hepatoprotective, anti-nociceptive effect, osteoarthritic, and anti-inflammation [13]. *Anethum graveloens* belongs to the Umbelliferae family which is otherwise known as Dill seeds. Which is used as one of the spices. *Anethum graveleons* extracts have a wide range of pharmacological effects including anti-inflammatory, antimicrobial, hypolipidemic, anti-diabetic, and anti-secretory effects [14]. The medicinal plant *Boerhavia diffusa* is mostly used for pain relief and infirmities and to treat inflammation, asthma, rheumatism, hepatitis, leucorrhea, blood pressure, urinary disorders and internal inflammation disorders. In addition, it has the ability of immunosuppressive as well as immuno-stimulatory ability, anticonvulsant, nephroprotective and antibacterial activity [15].

The current study focuses on identifying the principle phytocompound present in the polyherbal formulation, Erandadikwatham and its binding efficiency towards the targets TNF- α and HK-II through in-silico computational analysis. The phytocompounds that are scientifically reported to be present in the above mentioned plants were retrieved from the small molecule databases and their ADME prediction is examined. The molecules passed the ADME properties are subjected for molecular docking studies to evaluate their binding efficiency with the targeted proteins TNF- α and HK-II. The study received attention due to the adverse effects of the commonly used RA treatments, simultaneously Medicinal plants are getting more attention as a potential source of safe and cost-effective anti-rheumatic agents.

Herbs may be used as an effective alternative treatment for inflammatory diseases.

MATERIALS AND METHODS:

Data Retrieval: Polyherbal formulation Erandadi Kwatham contains five plants that includes Erandam (*Ricinus Communis*), Gokshuram (*Tribulus terrestris),* Rasna (*Alphinia galanga*), Satapushpa (*Anethum Graveolens*), Punarnava (*Boerhavia diffusa*). The phytocompounds present in each plants were listed from the literature resources that have been previously reported [16-27].

Structure Retrieval: The 2D structures of the phytocompounds were retrieved from the PubChem databases, and 3D structures of target proteins tumor necrosis factor-α (PDB ID:2az5) [28] and Hexokinase-II (PDB ID:2nzt) [29] were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank. TNF-α protein consist of 148 amino acid residues with four subunits (A,B,C&D) with the resolution of 2.10 Å and co-crystalized with the inhibitor 6,7-dimethyl–3 - [(methyl{2 -[methyl({1-[3-(trifluoro-methyl) phenyl]-1h-indol-3-yl}methyl) amino] ethyl}amino)ethyl] -4h-chromen -4-one and HK-II protein consist of 902 amino acid residues with two subunits (A&B), has a resolution of 2.45 Å with the co-crystalized ligand 6-O-phosphono-beta-D-glucopyranose and alpha-D-glucopyranose was bound to increase the stability of the protein.

ADME Analysis: Retrieved phytocompounds were subjected for ADME analysis using Qikprop module of Schrödinger. It predicts physicochemical properties and drug-likeness for the retrieved phytocompounds. The descriptors like QPlogS-predicted aqueous solubility, QPPCaco- predicted apparent Caco-2 permeability, QPlogBB predicted brain/blood partition coefficient Lipinski rule of 5 were predicted [30].

Ligand Preparation: Ligand preparation was performed using the LigPrep module of Schrödinger, by applying OPLS3e force field (Optimized potentials for liquid simulation). Integrated Epik module were employed to generate accurate, energy minimized 3D ligands, suitable for docking, by applying protonation and ionization states at pH 7.0 ± 0.4 physiological condition [31].

Protein Preparation: Protein preparation was performed by removing unwanted water molecules and hetero atoms, further added with polar hydrogen atoms, assigned partial charges using the OPLS-2005 force field, simultaneously partial energy was minimized [32].

Molecular Docking: Molecular docking analysis was carried out for 6 phytocompounds of Ayurvedic formulation Erandadikwatham. The ligands were docked with target protein TNF- α, and HK-II by using Glide module of Schrodinger software. Protein binding sites were predicted using sitemap tool. The binding affinity was determined with G score and the interactions of ligands with target proteins were visualized using PyMol viewer.

RESULTS:

ADME Analysis: Totally 100 compounds were subjected to the ADME analysis using Qikprop module to assess drug-likeness through various parameters like mol MW, donor hydrogen bond, acceptor hydrogen bond, QplogPwQPlogS, Qplog HERG, QPP MDCK, QPlogS- predicted aqueous solubility, QPPCaco- predicted apparent Caco-2 permeability, QPlogBB predicted brain/blood partition coefficient. Only 6 compounds satisfied the ADME properties, the compounds are: triethyl citrate (6506), butanedioic acid, hydroxyl- biethyl ester (24197), L-Valine, ethyl ester (87182), phenyl acetic acid (97942), 7trihydroxy-1-methyl-8-methylene, 1.4a-lactone, 10-methyl (539615), Pectolinarigenin (5320438) **Table 1.** Those compounds were used for the further molecular docking studies.

TABLE 1: ADME PROPERTIES AND DRUG-LIKENESS PREDICTION FOR PHYTOCOMPOUNDS

Compound	PubChem ID	mol MW	donor HB	accpt HB	Qplog Pw	QPlogS	Qplog HERG	QPP Caco	Qplog BB	Rule of five
Triethyl citrate	6506	276.286	0	5.75	5.545	-1.952	-3.653	624.27	-1.097	0
Butanedioic acid, hydroxyl. Diethyl ester	24197	190.196	0	4.7	5.125	-1.814	-4.24	465.988	-1.144	0
L-Valine, ethyl ester	87182	145.201	2	3	6.26	-0.303	-3.731	335.19	-0.017	0

Phenyl acetic acid	97942	218.295	1	2	5.284	-3.275	-2.047	389.9	-0.311	0
7trihydroxy-1-methyl —8-methylene, 1.4a-lactone. 10-methyl	539615	360.406	2	7.45	12.064	-3.281	-3.387	519.603	-0.709	0
Pectolinarigenin	5320438	314.294	1	4.5	8.569	-3.991	-5.118	589.572	-0.872	0

Molecular Docking: The Glide score and the phytocompounds interaction with target proteins TNF- α and HK-II were tabulated **Table 2.** The compound pectolinarigenin showed significant G. score for both the proteins and interactions. Molecular docking results reveals, that six ligands had an efficient binding with targeted protein TNF-α and 2d and 3d interactions were shown in **Fig. 1.** The **Fig. 1 (A)** illustrates that ligand triethyl citrate (6506) actively interacts through the hydrogen bond with the active site residues of the protein includes Ile-136 (bond length: 2.4 Å), Gln-25 (bond length - 2.1 Å), Leu-26 (bond length - 2.5 Å & 2.1 Å) and Asn-46 (bond length - 2.0 Å & 2.5 Å & 2.6 Å). Simultaneously, the hydrophobic interaction occurred with the residues Gln-24, Trp-28, Gln-47, asp-45, Ser-133, Ala-134, Arg-138, Gly-24 and Asn-137, with the G-score of -3.47. In **Fig. 1(B)** ligand hydroxyl diethyl ester (24197) has hydrogen bond interactions with the targeted protein, includes Gln-25(bond length - 2.4 Å), Leu-26 (bond length - 2.2 Å &2.2 Å), Ile-136 (bond length - 1.9 Å) and Asn-46 (bond length - 2.7 Å &2.4 Å). The amino acid residues involved in the hydrophobic interactions including Gln-27, Gly-24, Aln-137, Ala-134, Gln-47, Asp-45 and Ser-133. G-score of the respective protein was found to be -3.40 kcal/mol. **Fig. 1(C)** illustrates that ligand makes one hydrogen bond with the amino acid residues Ile-136 (bond length – 2.1 Å), hydrophobic interactions involves a amino acid residues Gly-24, Asn-137, Gln-25, Asn-46, Trp-28, Ala-134 and Ser-133. The Docking results reveals that the ligand L-Valine, ethyl ester (87182) has a G-score of -3.37 kcal/mol. **Fig. 1(D)** depicts that the ligand Phenylacetic acid (97942) had an hydrogen bond interaction with residue Gln-25 (bond lenghth-2.1 Å) with the binding energy of -3.35 kcal/mol and had an hydrophobic interactions with the Als-134, Ser-133, Gln-47, Asp-45, Ile-136, Leu-26, Pro-139 and Gly-24. In **Fig. 1(E),** that the ligand 7trihydroxy-1-methyl-8-methylene, 1.4a-lactone, 10-methyl (539615) made a three hydrogen bond interactions with the residues Asp-45 (bond length- 2.6 Å), Asn-46 (bond length-2.1 Å), and Ile-136(bond length-2.1 Å), with a binding energy of -2.17 kcal/mol, on the other hand hydrophobic interaction involves Ser-133, Gln-47, Gly-24, Gln-25, pro-139 and Asn-137. The ligand Pectolinarigenin (5320438) has two hydrogen bond interactions with the residues Asp-45 (bond length-1.8 Å) and Leu-26 (bond length-2.2 Å), hydrophobic interaction made with the amino acid residues such as Lys-90, Gln-47, Asn-46, Gln-25, Asn-137and Gly-24 with a binding energy of -1.56 kcal/mol as shown in **Fig. 1(F).**

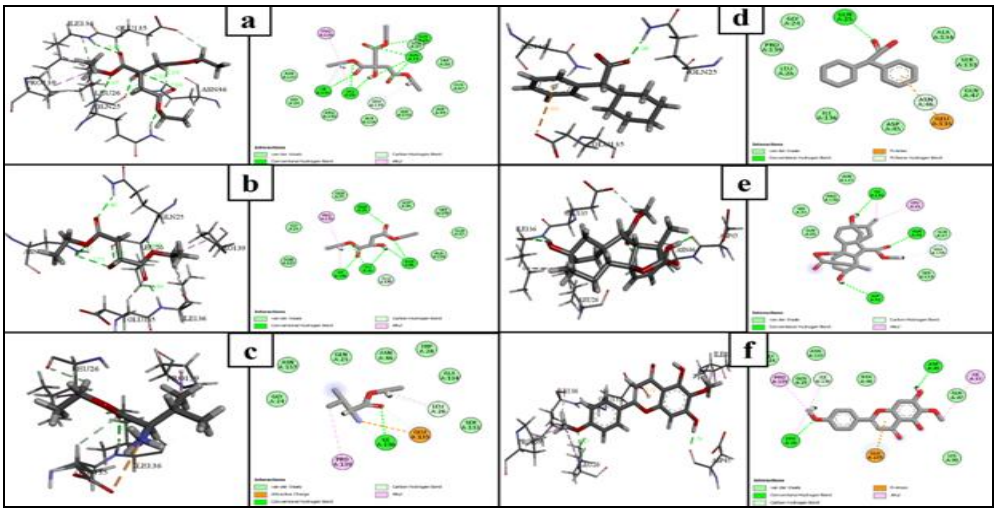

FIG. 1: RESULTS OF THE MOLECULAR DOCKING WITH THE PROTEIN TNF- A. 2D&3D INTERACTION WERE SHOWN. A. TRIETHYL CITRATE B. BUTANEDIOIC ACID, HYDROXYL. DIETHYL ESTER C. L-VALINE, ETHYL ESTER D. PHENYLACETIC ACID E. 7TRIHYDROXY-1-METHYL —8-METHYLENE, 1.4A-LACTONE. 10-METHYL F. PECTOLINARIGENIN

Subsequently, Docking studies were also employed for the targeted protein HK-II, results were shown in **Table 3** and **Fig. 2(A)** illustrates the interaction between the targeted protein HK-II and ligand triethyl Citrate (6506), that ligand and protein formed hydrogen bond with the amino acid residues Arg-69 (bond length-1.8 Å & 1.9 Å), Phe-67 (bond length-2.0 Å), and Leu-163(bond length-2.2 Å), including the hydrophobic interacting residues Ser-70, Val-68, Ala-460, Ala-464, Ile-203, Asp-814 and Met-255. The G-Score of protein HK-II and ligand triethyl Citrate (6506) was found to be -4.24 kcal/mol.

TABLE 2: MOLECULAR DOCKING ANALYSIS OF PHYTOCOMPOUNDS WITH THE TARGET PROTEINS TNF- A AND HK-II

Compound Name and ID	TNF- α			HK-II		
	G score (Kcal/mol)	Interaction residues	Bond length (Å)	G score (Kcal/mol)	Interaction residues	Bond length (Å)
		ILE-136	2.4	-4.24	ARG-69	1.8 & 1.9
		GLN-25	2.1		PHE-67	2.0
6506	-3.47	LEU-26	2.5&2.1		LEU-163	2.2
		ASN-46	2.0& 2.5& 2.6			
24197		GLN-25	2.4	-3.96	ARG-69	2.0 & 2.5
	-3.40	LEU-26	2.2&2.2		PHE-67	2.0
		ILE-136	1.9		LEU-163	2.0
		ASN-46	2.7,2.4			
87182	-3.37	ILE-136	2.1	-3.29	ARG-69	2.1,1.9
97942	-3.35	GLN-25	2.1	-3.32	ARG-69	1.7
		ASP-45	2.6	-3.73	ASP-814	1.7
539615	-2.17				LEU-463	2.0
		ASN-46	2.1		LYS-162	2.7
					ARG-470	2.6
		ILE-136	2.1		ARG-69	2.8
5320438	-1.56	ASP-45	1.8	-5.88	LEU-163	2.0
					ASP-164	2.1
		LEU-26	2.2		LEU-463	2.2

In **Fig. 2(B)** the ligand Butanedioic acid, hydroxyl. Diethyl ester (24197) has five hydrogen bond interactions with the amino acid residues namely Arg-69 (bond length-2.0 & 2.5 Å), Phe-67(bond length 2.0 Å), and Leu-163(bond length-2.0 Å) and hydrophobic interactions occurs between Ala-464, Met-255, Asp-814, Ala-460 and Ile-203. Ligand Butanedioic acid, hydroxyl. Diethyl ester (24197) binding affinity with the protein HK-II was calculated as -4.24 kcal/mol. Furthermore, the **Fig. 2(C)** reveals that the ligand . L-Valine, ethyl ester (87182) has two hydrogen bond interactions with residues ARG-69 (bond length- 2.1,1.9 Å), hydrophobic interactions with residues Thr-161, Val-459 and Leu-163 and one salt bridge interaction was occurred with Asp-814. Binding affinity with the protein was found to be -3.29 kcal/mol. **Fig. 2(D)** depicts that ligand Phenylacetic acid (97942) not directly interacted with the protein through hydrogen bond. Conversely, salt bridge was occurred between protein and ligand, due to absence of hydrogen bond the interaction might be not stable for the long time. Residues Met-255, Ala-460, Ile-203, Ala-464, Ile-817 and Thr-161 involves hydrophobic interactions. Binding affinity was assessed as -3.32 kcal/mol. **Fig. 2(E)** reveals that ligand 7trihydroxy-1-methyl-8-methylene, 1.4a-lactone. 10-methyl (539615) interacts with five hydrogen bond with the protein, the interaction occurred between the amino acid residues such as Leu-463(bond length-2.0 Å), Arg-470(bond length-2.7 Å), Asp-814(bond length-1.7 Å), Arg-69 (bond length-2.8 Å) and lys-162(bond length-2.7 Å) followed by hydrophobic interactions involves Ala-460, Asp-164, Leu-163, Phe-67, Thr-161 and Ile-817. The binding affinity was calculated as -3.73 kcal/mol. **Fig. 2F)** depicts, that ligand Pectolinarigenin (5320438) interacts with the targeted protein through three hydrogen bonds with the amino acid residue leu-163 (bond length-2.0 Å), Asp-164(bond length- 2.1 Å) and Leu-463(bond length- 2.0 Å). Hydrophobic interaction involves the Ala-460, His-467, Ile-817, Leu-797, Met-242, Gly-250, Arg-69, Val-248, Phe-67 and Thr-161. Binding affinity with the protein was calculated as -5.88 kcal/mol.

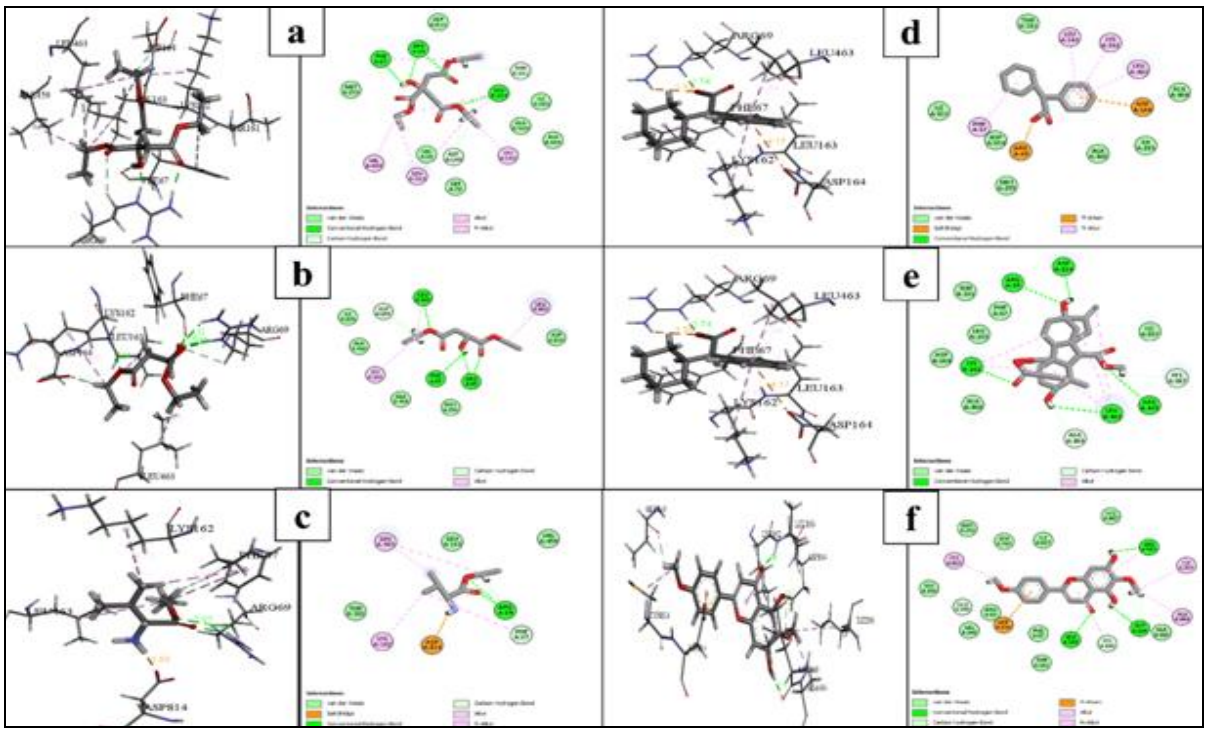

FIG. 2: RESULTS OF THE MOLECULAR DOCKING WITH THE PROTEIN HK-II. 2D&3D INTERACTION WERE SHOWN A. TRIETHYL CITRATE (6506), B. BUTANEDIOIC ACID, HYDROXYL. DIETHYL ESTER (24197), C. L-VALINE, ETHYL ESTER (87182), D. PHENYLACETIC ACID (97942), E. 7TRIHYDROXY-1-METHYL —8-METHYLENE, 1.4A-LACTONE. 10-METHYL(539615), F. PECTOLINARIGENIN (5320438)

DISCUSSION: Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by synovial joint inflammation, cartilage degradation, and progressive bone erosion, leading to persistent pain and functional impairments. Although the precise pathogenesis of RA remains incompletely understood, immune cell infiltration primarily by macrophages, fibroblast-like synoviocytes (FLS), dendritic cells, T and B lymphocytes, and neutrophils plays a key role in disease progression. Among the pro-inflammatory cytokines involved, tumor necrosis factor-alpha (TNF-α) is a major contributor to RA pathology, promoting synovial fibroblast activation and collagenase synthesis, which accelerate cartilage damage and joint destruction [34]. Additionally, hexokinase-II (HK-II), a key enzyme in glucose metabolism, has been implicated in the dysregulated metabolic environment of RA-affected joints [35, 36].

The present study investigated the potential therapeutic effects of six phytocompounds from the polyherbal formulation Erandadi Kwatham by evaluating their binding efficiency against TNF-α and HK-II through molecular docking studies. The results identified these six compounds as strong lead candidates with promising drug-like properties. Docking analysis revealed significant binding affinities between these phytocompounds and the target proteins, with TNF-α (PDB: 2AZ5) exhibiting binding scores of -3.47 (6506), -3.40 (24197), -3.37 (87182), -3.35 (97942), -2.17 (539615), and -1.56 (5320438). Similarly, the compounds demonstrated high affinity toward HK-II (PDB: 2NZT) with binding scores of -4.24 (6506), -3.96 (24197), -3.29 (87182), -3.37 (97942), -3.73 (539615), and -5.88 (5320438). These findings suggest that the phytocompounds may effectively inhibit both TNF-α and HK-II, thereby mitigating RA-associated inflammation and metabolic dysregulation.

Several medicinal plants present in Erandadi Kwatham contribute to its therapeutic potential against RA. Ricinus communis, widely distributed in tropical regions, possesses significant anti-inflammatory properties and has been traditionally used for treating musculoskeletal disorders, including arthritis and rheumatism. Its flavonoid-rich composition contributes to its strong anti-inflammatory activity. *Tribulus terrestris*, known for its high saponin content, has demonstrated anti-RA effects by inducing apoptosis in RA-FLS and reducing pro-inflammatory cytokine levels via the

MAPK signaling pathway. *Alpinia galangal* has been shown to alleviate rheumatic inflammation by inhibiting key inflammatory mediators such as TNF-α, IL-6, IL-1, and COX-2, further supporting its potential as an anti-arthritic agent [38].

Boerhavia diffusa, a well-documented Ayurvedic herb, has exhibited strong anti-inflammatory properties by inhibiting sPLA2, a crucial enzyme in the eicosanoid pathway responsible for generating inflammatory lipid mediators. Its ability to prevent edema and pain suggests its effectiveness in managing inflammatory disorders, including RA. Anethum graveolens, traditionally used as both a spice and medicinal herb, has demonstrated the ability to suppress inflammatory cytokines such as TNF-α and IL-1β, as well as inhibit nitric oxide production, making it a potential candidate for RA treatment [39, 40].

The molecular docking studies conducted in this research confirm that the bioactive compounds in Erandadi Kwatham exhibit strong binding affinity for TNF-α and HK-II, with favorable ADME (Absorption, Distribution, Metabolism, and Excretion) properties. These findings highlight the potential of this polyherbal formulation as a therapeutic intervention for RA. However, while *in-silico* analyses provide valuable insights, further *in-vitro* and *in-vivo* validation, along with clinical trials, are essential to establish the efficacy, safety, and pharmacokinetic properties of these compounds before considering them for clinical use.

CONCLUSION: This *in-silico* study evaluated the therapeutic potential of various phytocompounds from Erandadi Kwatham in targeting Rheumatoid Arthritis (RA) through inhibition of the inflammatory cytokine TNF-α and the metabolic modulator HK-II. Among the six identified bioactive compoundstriethyl citrate (6506), butanedioic acid, hydroxyl diethyl ester (24197), L-Valine, ethyl ester(87182), phenylacetic acid (97942), 7-trihydroxy-1-methyl-8-methylene-1,4a-lactone-10-methyl (539615), and pectolinarigenin (5320438), both triethyl citrate and pectolinarigenin demonstrated strong drug-likeness properties and favorable ADME profiles. Molecular docking analysis further revealed that these compounds exhibit significant binding affinities with TNF-α and HK-II, suggesting their potential as effective therapeutic agents for RA. However, while these findings provide promising insights, further *in-vitro* and *in-vivo* studies are necessary to validate their biological efficacy and safety before clinical application.

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CONFLICTS OF INTEREST: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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