Natural Resources for Human Health

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Received 30 December 2025
Revised 16 March 2025
Accepted 16 June 2026
Available Online 11 August 2026

Edited by Shafi Ullah Khan

KEYWORDS:
Rheumatoid arthritis
Molecular docking
Phytocompounds
Network pharmacology
Leea indica

Natr Resour Human Health 2026; 6 (4): 281–298
https://doi.org/10.53365/nrfhh/224630
eISSN: 2583-1194

Network pharmacology analysis of Leea indica against rheumatoid arthritis: in-silico studies

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ABSTRACT: Background: Rheumatoid arthritis (RA) is a long-term inflammatory disease. The potential therapeutic benefits of natural products in modifying the inflammatory pathways linked to RA have drawn increasing attention. Purpose: The objective of this study was to determine the anti-inflammatory property of *Leea indica* using network pharmacology and molecular docking techniques. Methodology: Bioactive compounds of *Leea indica* were identified using public phytochemical databases. Network pharmacology analysis was conducted to determine RA-associated genes and construct a compound–target–disease interaction network. Enrichment analysis identified key signalling pathways involved in inflammation, particularly NF-κB and cytokine-mediated pathways. Molecular docking was performed to evaluate the binding affinity of major phytocompounds with RA-related protein targets. In addition, qualitative phytochemical screening was carried out to identify major secondary metabolites in the leaf extract. The antioxidant potential of the extract was evaluated using the phosphomolybdenum (PM) assay and the egg albumin denaturation inhibition assay for anti-inflammatory properties. Results: Phytochemical analysis verified the existence of multiple bioactive compounds. The egg albumin denaturation assay also showed increasing anti-inflammatory activity, reaching 85.23% inhibition at 300 µL. Network pharmacology analysis revealed that multiple *Leea indica* compounds strongly interacted with RA-associated targets. Pathway enrichment highlighted significant involvement of inflammation-related pathways, including NF-κB, TNF, and IL-17 signalling. Among the compounds, kaempferol-3-O-arabinoside exhibited strong binding with caspase-3 (–9.23 kcal/mol) and GAPDH (–10.17 kcal/mol), suggesting a role in apoptotic and metabolic regulation. Catechin gallate also demonstrated strong binding with AKT1 (–9.4 kcal/mol). Conclusion: The findings of the study support the plant as a promising candidate for further pharmacological investigation.

1. INTRODUCTION

RA, a chronic inflammatory joint condition, can lead to bone and cartilage loss as well as disability. For patients with well-defined risk factors for unfavourable outcomes, such as high disease activity, autoantibodies, and early joint injury, early diagnosis is critical to achieving the best possible therapeutic outcome. Utilizing a therapy-to-target approach, assessing disease activity with composite indices, and using traditional, biological, and novel non-biological disease-modifying antirheumatic medications are all part of

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treatment algorithms (Smolen et al., 2023). An enormous burden is placed on both the individual and society by RA, a chronic illness (Safiri et al., 2021; Burmester & Pope, 2022; Almutairi et al., 2021; Taylor et al., 2021; Smolen et al., 2023). Musculoskeletal disorders lead to an individual burden that includes a decline in quality of life, physical function, and cumulative concomitant risk (Burmester & Pope, 2022). Apart from significant upfront medical expenses, functional disability, diminished employment capacity, and lower social participation result in a socioeconomic burden (Safiri et al., 2021). It is crucial to make an early diagnosis, start treatment right away, and develop creative treatment plans to manage the infection and lessen or avoid the resulting harm. The incidence of RA ranges from 0·5% to 1%, and it appears to decline from urban to rural locations as well as from north to south in the northern hemisphere (Safiri et al., 2021; Almutairi et al., 2021; Finckh et al., 2022). There are some highly prevalent Native American populations. RA is a chronic autoimmune disease characterized by joint inflammation and cartilage degradation. Current therapies are limited by side effects and incomplete efficacy, highlighting the need for new approaches. Natural products such as *Leea indica*, traditionally used for inflammatory conditions, may provide novel bioactive compounds. This study applies network pharmacology and molecular docking to explore their potential interactions with RA-related targets (Zheng et al., 2022).

Leea indica is currently classified as a species within the genus *Leea*, which is placed in the Vitaceae family, despite its previous placement in the separate Leeaceae family (Plants of the World Online [POWO], 2024). There are numerous medicinal benefits associated with the pharmacological characteristics of *Leea indica*. Research suggests that *Leea indica* may be used as a treatment for a number of ailments because it possesses analgesic, antidiabetic, anti-inflammatory, antibacterial, antioxidant, and antiproliferative properties (Khuniad et al., 2022). Alkaloids, flavonoids, polyphenolics, and terpenoids have been identified through phytochemical investigations as the main bioactive components of *Leea indica*, thereby supporting the plant's traditional medicinal applications (Khuniad et al., 2022). Research has indicated that leaf extracts from *Leea indica* possess antioxidative, antibacterial, and cytotoxic properties, indicating their potential for use in medicinal applications. To further emphasise the many medicinal uses of *Leea indica*, it has also been traditionally used to treat wounds, rheumatism, diabetes, pyrexia, and asthma. Due to its bioactive components and historical applications, *Leea indica* appears to have substantial medicinal potential overall, according to scientific research (Khuniad et al., 2022).

Network pharmacology (NP) is a novel approach to drug discovery that focuses on the intricate interactions among drugs, biological targets, and diseases. It challenges the traditional "one drug, one target" approach, which often results in high failure rates in clinical trials. By integrating biological data, NP offers a comprehensive understanding of drug interactions with multiple targets, thereby enhancing therapeutic efficacy and minimizing side effects (Zheng et al., 2022). It is particularly useful in studying traditional medicine systems such as Traditional Chinese Medicine (TCM), as it validates complex herbal formulations and identifies active compounds (Wang et al., 2022). It also facilitates drug repurposing by uncovering new therapeutic uses for existing drugs through biological network analysis. Furthermore, it can predict potential side effects and adverse reactions, thereby ensuring safety and efficacy. Its integration with genomic technologies supports personalized medicine strategies, allowing treatments to be tailored based on individual patient profiles and unique biological networks (Hopkins, 2021). Although network pharmacology and docking have been widely applied to natural compounds in RA, most studies have focused on single phytochemicals or well-characterized plants. In contrast, our study evaluates the multi-target binding profile of *Leea indica*, a plant with limited prior mechanistic exploration in RA, thereby expanding the scope of phytopharmaceutical research in this disease.

2. METHODOLOGY

2.1. Collection and preparation of plant materials

The leaves of *Leea indica* were collected from Medicinal Live in Karnataka. The fresh plant material was dried at room temperature, crushed into a powder using a lab blender, and then soaked in 1:20 (w/v) ethanol. After centrifugation at 12,000 rpm for 15 minutes, the mixture was filtered. The crude ethanol extract was obtained by air-drying the resulting filtrate.

2.2. Determination of secondary metabolites by Phytochemical analysis

The leaf extract of *Leea indica* was qualitatively tested for secondary metabolites, including alkaloids, flavonoids, phenols, saponins, tannins, proteins and amino acids, phenolic compounds, cardiac glycosides, and reducing sugars, using the method described by Shaikh and Patil (2020).

2.3. Determination of antioxidant activity by Phosphomolybdenum assay

The total antioxidant activity was estimated using the phosphomolybdenum (PM) assay. The reaction mixture was incubated at 95°C for 90 minutes, and the absorbance was measured at 695 nm. Ascorbic acid was used as the reference standard (Kumar, 2021).

2.4. Determination of anti-inflammatory activity by Egg albumin denaturation assay

The technique described by Sakib (2021) was used to assess the inhibition of protein denaturation assay. Egg albumin (0.2 mL), phosphate-buffered saline (PBS, pH 6.4; 2.8 mL), and *Leea indica* leaf extract (2 mL) or distilled water (control) were combined to create a 5 mL reaction mixture. After incubation at 70°C for 10 minutes, the absorbance at 660 nm was measured in comparison with that of a blank.

2.5. Screening of components in *Leea indica*

The outline of the network pharmacology approach is shown in Figure 3. The bioactive compounds were retrieved from the literature and the PUBMED (https://pubmed.ncbi.nlm.nih.gov/) database. The selected compounds were studied using SWISSADME (http://www.swissadme.ch/) by evaluating drug-likeness and physicochemical properties, and the compounds were retained if they satisfied the drug-likeness criteria (Lipinski's rule of five), solubility threshold (LogS > −4), and favourable ADMET properties. This ensured that only compounds with plausible pharmacokinetic profiles were included for docking analysis. Compound–target interactions were obtained from SwissTargetPrediction release 2025.1, accessed during the study period in 2025 (www.swisstargetprediction.ch) (Sakle et al., 2020)

2.6. Acquiring target genes for RA

Gene–disease associations were retrieved from DisGeNET (https://disgenet.com/), version 7.0, accessed during the study period in 2025. Specifically, 2000 targets were identified by searching the keyword "rheumatoid arthritis." From these, only high-confidence associations (DisGeNET score > 0.1) were retained. Duplicates were removed after mapping to UniProt IDs, resulting in the final set of targets used for network construction. Because database content is regularly updated, the reported associations reflect the versions specified here to ensure reproducibility (Piñero et al., 2020; The UniProt Consortium, 2023).

2.7. Establishing a disease-targeting network

Cytoscape (version 3.10.4) was used to import the CSV files containing the compound–target and target–disease relationships. Compounds, targets, and diseases were represented by nodes, while interactions between compounds and targets or between diseases and targets were represented by edges. The Cytoscape plugin NetworkAnalyzer was used for network analysis, and hub nodes were identified by calculating quantitative metrics such as degree and betweenness centrality. To shed light on the therapeutic mechanisms underlying the treatment of RA, a network depicting these interactions was created (Figure 4A). Many targets were found to be affected by a variety of compounds, suggesting that the active biochemicals in *Leea indica* may work in coordination. File formats, node and edge definitions, plugins, and quantitative parameters were defined to create a transparent and reproducible compound–target–disease network (Shang et al., 2022).

2.8. Target PPI network construction and analysis

A Venn diagram was created as displayed in (Figure 4B) to illustrate the intersections between RA and *Leea indica* using InteractiVenn. Protein–protein interactions (PPIs) were analysed using STRING (version 11.0, https://string-db.org/) as presented in Figure 4C. A maximum confidence score (0.900) was selected to ensure high-quality interactions while minimizing false positives. Disconnected nodes were excluded from the final PPI network to focus on meaningful interactions. The network was visualized using Cytoscape 3.10.4 and is represented in Figure 4D (Sakle et al., 2020). Red nodes denoted the highest rank, followed by downward colour changes, and the colour-rank approach was used to identify the top 10 hub proteins from the compound–target–disease network built in Cytoscape. Since these proteins represent important nodes with possible biological significance in the pathophysiology of RA, they were prioritized for docking. Molecular docking studies were performed using the relevant PDB IDs for these proteins obtained from the STRING database.

2.9. Molecular docking

Protein structures were obtained from the RCSB Protein Data Bank, and phytocompound structures were retrieved

from the PubChem database (Kim et al., 2023). Open Babel software was used to convert ligands from SDF to PDB format, followed by energy minimization. AutoDock Tools 1.5.6 was employed for docking studies. During protein preparation, water molecules were removed, polar hydrogens were added, and Gasteiger charges were assigned. Docking was performed using standardized parameters, with the grid box centred on the active site (coordinates: X, Y, Z; dimensions: X Å × Y Å × Z Å). Multiple docking runs were executed with an exhaustiveness parameter of N to ensure convergence. Hydrogen bonds, hydrophobic contacts, and other non-covalent interactions were the main focus of the visualization of binding interactions in Discovery Studio. A limitation of the current study is that these interactions were not directly compared with the binding mechanisms of recognized RA treatments. In addition, redocking of cocrystallised ligands and RMSD validation were not conducted in this study, which is also a limitation. Future work will address these steps to strengthen the reliability of docking predictions.

3. RESULTS

3.1. Phytochemical analysis

Preliminary phytochemical screening of the *Leea indica* ethanol extract revealed the presence of several bioactive constituents (Table 1). In the table, the symbols +, ++, and +++ indicate weak, moderate, and strong presence of phytochemicals, respectively, while – indicates the absence or non-detectable levels of the compounds in the extract. The analysis confirmed the presence of alkaloids (+), flavonoids (++), saponins (+++), reducing sugars (+++), and cardiac glycosides (+) in the ethanol extract. Alkaloids are known for their analgesic, antimicrobial, and anti-inflammatory properties, while flavonoids are widely recognized for their strong antioxidant and free radical scavenging activities. Saponins possess anti-inflammatory, immunomodulatory, and antimicrobial effects, and cardiac glycosides are reported to have cardioprotective and potential anticancer activities. The presence of these phytochemicals suggests that *Leea indica* contains compounds capable of contributing to its biological activities.

However, phenols, tannins, proteins and amino acids, and certain phenolic compounds were not detected in the extract under the present experimental conditions. Overall, the presence of these bioactive phytochemicals may be responsible for the observed antioxidant and anti-inflammatory activities of the plant extract.

Table 1
Preliminary phytochemical screening of *Leea indica* leaf extracts. This table shows the presence of several bioactive compounds. Alkaloids tested positive with Dragendorff's and iodine tests, while flavonoids showed a strong positive reaction with ferric chloride. Saponins and reducing sugars were strongly present, indicated by the foam and Benedict's tests. Cardiac glycosides were detected through the Keller–Killani test. However, phenols, tannins, proteins and amino acids, and phenolic compounds showed negative results, indicating their absence or very low concentration.

S. No	Constituent	Test	Observations
1	Alkaloids	Draggendorf's	+
		Iodine	+
2	Flavonoids	Ferric chloride	+ +
		Conc. H_2SO_4	-
3	Phenols	Iodine	-
4	Saponins	Foam	+ + +
5	Tannins	Lead acetate	-
6	Reducing sugar	Benedict's	+ + +
7	Proteins & Amino acids	Xanthoproteic	-
8	Cardiac glycosides	Keller-killani	+
9	Phenolic compounds	Lead acetate	-

3.2. Phosphomolybdenum antioxidant assay

The antioxidant activity of *Leea indica* leaf extract was evaluated using the phosphomolybdenum (PM) assay and compared with the standard ascorbic acid. The extract exhibited a concentration-dependent increase in total antioxidant capacity (TAC). The TAC values for the extract increased from 51% at 100 µg/mL to 78% at 300 µg/mL. In comparison, the standard ascorbic acid showed higher antioxidant activity, with TAC values ranging from 81% at 100 µg/mL to 90% at 300 µg/mL concentrations. Overall, although the antioxidant activity of *Leea indica* was lower than that of the standard, the extract demonstrated considerable antioxidant potential, which may be attributed to the presence of phytochemicals such as flavonoids and alkaloids detected during the phytochemical screening (Figure 1).

3.3. Egg albumin denaturation inhibition assay

The anti-inflammatory activity of *Leea indica* leaf extract was evaluated using the egg albumin denaturation inhibition assay. The extract showed a concentration-dependent increase

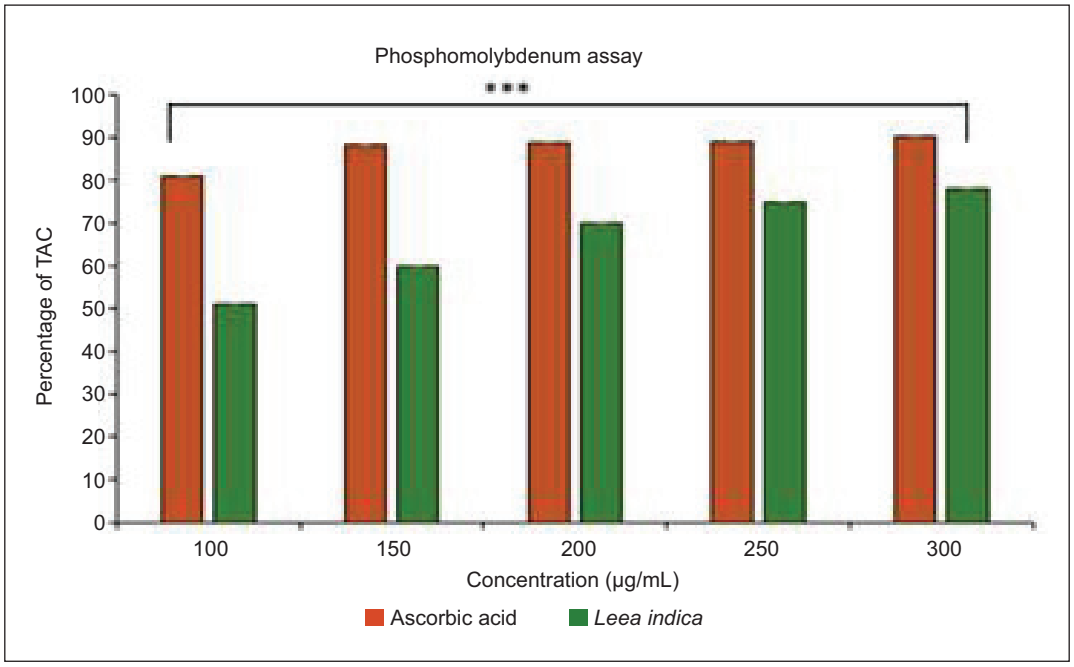

Figure 1. The figure shows the antioxidant activity of *Leea indica* leaf extract compared with ascorbic acid using the phosphomolybdenum (PM) assay. The antioxidant activity of the extract increased with increasing concentration (100–300 µL), indicating a dose-dependent effect. However, ascorbic acid showed higher antioxidant activity at all concentrations. Error bars represent the standard deviation of triplicate measurements.

in percentage inhibition. The inhibition values increased from 40% at 100 µg/mL to 85% at 300 µg/mL. The standard drug indomethacin also exhibited increasing inhibition with increasing concentration, showing values ranging from 18% at 100 µg/mL to 83% at 300 µg/mL. The results indicate that the *Leea indica* extract demonstrated strong inhibition of protein denaturation at higher concentrations, comparable to the standard drug, suggesting significant anti-inflammatory potential (Figure 2).

3.4. SWISSADME-guided compound screening in *Leea indica*

According to the SWISSADME analysis, the bioactive compounds found in *Leea indica* were selected based on their favourable drug-likeness and physicochemical characteristics. Compounds with anti-inflammatory and antioxidant properties, such as gallic acid, kaempferol, and ellagic acid, were retained because of their potential therapeutic value in RA. Myricetin 3-O-rhamnoside and epigallocatechin-3-O-gallate are two additional compounds that possess immunomodulatory properties, further supporting their potential use in the treatment of RA. The application of SWISSADME enhanced the possibility of *Leea indica* having multi-targeted effects beneficial for RA treatment by enabling the targeted selection of molecules with ideal pharmacokinetic characteristics, as represented in Table 2. The ADMET and predicted pharmacokinetic characteristics of bioactive substances from *Leea indica* that may have anti-rheumatoid arthritis effects were also evaluated. The in silico profiles confirmed the compounds' potential for safety and drug-likeness by showing that the majority exhibited good intestinal absorption, no hepatotoxicity, and no CYP2D6 interaction, as listed in Table 3.

3.5. Active ingredient-target network

The complex interactions between bioactive compounds and target genes linked to RA are depicted in Figure 4A, which shows the active ingredient–target network for *Leea indica*. This network visualization enables the identification of several bioactive substances that interact with a range of RA-related targets, suggesting that these compounds may exert therapeutic benefits through a variety of molecular mechanisms. Notably, substances such as gallic acid, ellagic acid, and kaempferol are connected to several targets, indicating their pivotal role in regulating immunological and inflammatory pathways essential to the pathogenesis of RA.

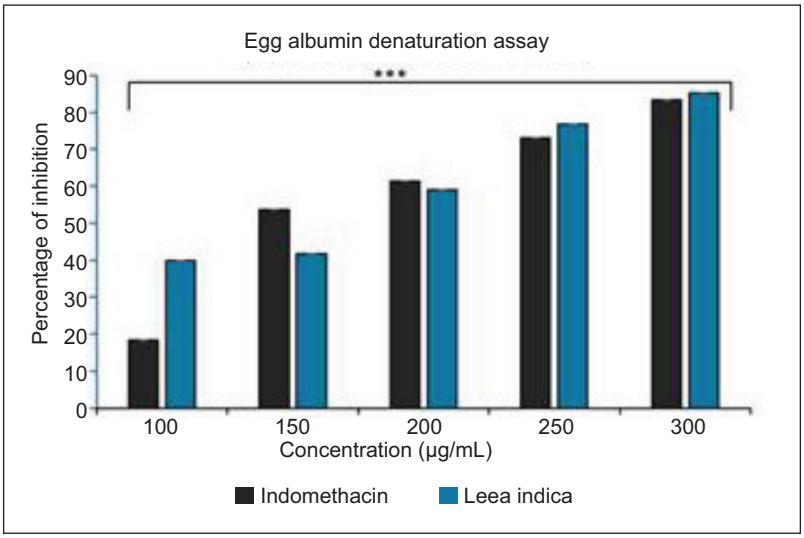

Figure 2. The figure shows the anti-inflammatory activity of *Leea indica* leaf extract compared with the standard drug indomethacin using the egg albumin denaturation inhibition assay. The inhibition activity increased with increasing concentration (100–300 µL) for both the extract and the standard. At higher concentrations, the *Leea indica* extract exhibited comparable inhibition to indomethacin. Error bars represent the standard deviation of triplicate measurements.

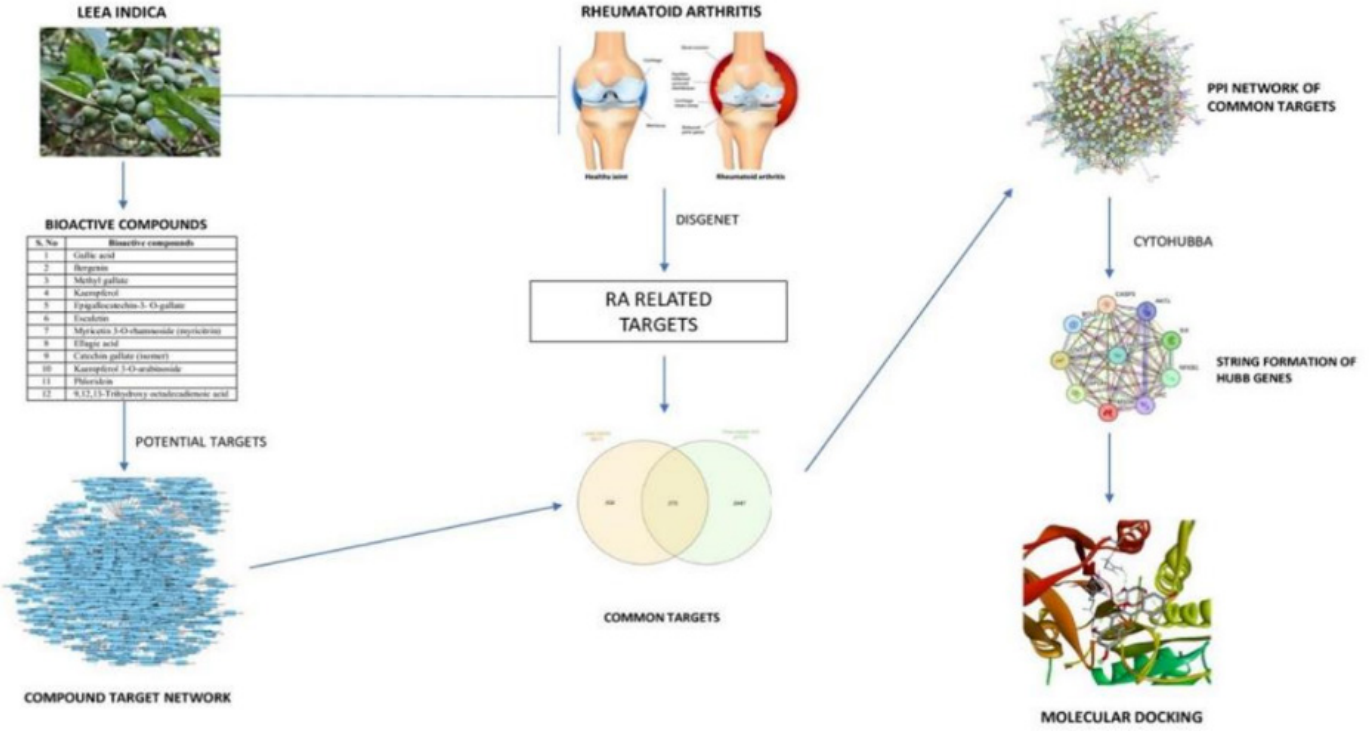

Figure 3. Schematic workflow of network pharmacology and molecular docking analysis of *Leea indica* against rheumatoid arthritis. The figure illustrates the workflow of the study, beginning with the identification of bioactive compounds from *Leea indica* and their potential targets. These targets are compared with RA-related genes to identify common targets. A compound–target network is then constructed and analyzed using Cytoscape, followed by PPI network analysis and hub gene identification. Finally, molecular docking is performed to validate the interactions between key compounds and RA-related target proteins.

Table 2
List of bioactive compounds were identified from *Leea indica* based on favourable drug-likeness and physicochemical characteristics. This table lists twelve bioactive compounds isolated from *Leea indica* through database mining. These phytochemicals were selected based on their known or predicted pharmacological relevance. They were used for target prediction, network pharmacology analysis, and molecular docking to assess their potential role in treating RA.

S. No	Bioactive compounds
1	Gallic acid
2	Bergenin
3	Methyl gallate
4	Kaempferol
5	Epigallocatechin-3-O-gallate
6	Esculetin
7	Myricetin 3-O-rhamnoside (myricitrin)
8	Ellagic acid
9	Catechin gallate (isomer)
10	Kaempferol 3-O-arabinoside
11	Phloridzin
12	9,12,13-Trihydroxy octadecadienoic acid

The possibility of multitarget modulation is highlighted by the existence of multi-target interactions, in which various bioactive compounds may work together to improve therapeutic efficacy by simultaneously modifying multiple biological pathways related to inflammation, oxidative stress, and immunological response. In complex illnesses such as RA, where single-target medicines frequently fail, such a multitargeted strategy is beneficial. Additionally, this network study suggests that *Leea indica* may have therapeutic effects beyond RA, including effects on pathways connected to other inflammatory or immune-related illnesses.

3.6. Intersection of active compounds and RA-related targets

The Venn diagram shown in Figure 4B demonstrates the potential of *Leea indica* bioactive compounds as a multitarget treatment approach for RA. By interacting with various RA-relevant pathways, these compounds may produce cumulative or complementary effects, potentially improving overall treatment efficacy. *Leea indica*-based medicines may treat not only the symptoms but also the fundamental processes driving disease development. Its ability to target multiple pathways implies a multilayered strategy for managing RA, addressing systemic symptoms beyond joint inflammation. Common targets may also be relevant to other autoimmune or inflammatory diseases, thereby expanding the potential therapeutic applications of *Leea indica* beyond RA. This convergence of compounds and targets makes it a promising option for further investigation in the management of complex disorders such as RA.

3.7. PPI network analysis of RA-related targets in *Leea indica*

Figure 4C illustrates the PPI network, which shows important connections between RA-associated targets and provides valuable information about how the bioactive compounds in *Leea indica* may affect the interrelated protein pathways implicated in RA. This high-confidence analysis identifies key nodes that may serve as focal points for therapeutic modulation, suggesting that these substances may act by targeting critical proteins within these networks. Cytoscape was further used to visualize the PPI network, with a focus on node degree to identify hub proteins, namely those with a high degree of connectivity (Figure 4D). Given that they are important sites of interaction within the RA network, these hub proteins are likely to play essential roles in disease regulation. By mapping these high-degree nodes, the visualization provides insight into the potential systemic effects of *Leea indica* components, which may influence multiple pathways and support a more comprehensive treatment approach for RA. Thus, this PPI network study highlights the capacity of *Leea indica* to alter intricate protein interactions both locally and systemically, pointing to a viable approach for addressing the complex nature of RA.

3.7. Binding energy profiles of *Leea indica* bioactives

Table 4 displays the binding energy analysis of the bioactive compounds found in *Leea indica*. The analysis shows that these compounds have distinct affinities for various RA-related protein targets. Binding energies were interpreted as relative indicators of interaction strength. To provide biological context, the values were compared with ranges reported in the literature for small-molecule inhibitors of RA-related proteins, highlighting that affinities around −9 kcal/mol fall within the range of known modulators. Compounds with negative binding energy values exhibit stronger and more stable interactions, suggesting higher therapeutic potential. Certain compounds consistently showed favourable binding energies with multiple targets, indicating their potential in modulating RA-related pathways. These findings highlight the plant's multitarget capability, with high-affinity compounds potentially playing a crucial role in addressing various aspects of RA by interacting with proteins involved in disease progression.

Table 3

Represent the predicted Pharmacokinetic and ADMET properties of bioactive compounds from *Leea indica* with potential activity against rheumatoid arthritis. The table presents in silico pharmacokinetic and ADMET profiles of selected Leea indica compounds with potential anti-rheumatoid arthritis activity. Most compounds exhibited good intestinal absorption, non-hepatotoxicity, and lacked CYP2D6 interaction, indicating a favourable safety and drug-likeness profile.

	Compounds	Gallic acid	Bergenin	Methyl gallate	Kaempferol	Epigallocatechin-3-O-gallate	Esculetin	Myricetin 3-O-rhamnoside	Ellagic acid	Catechin gallate	Kaempferol 3-O-arabinoside	Phloridzin	9,12,13-Trihydroxy octadecadienoic acid
Toxicity	Oral rat acute toxicity (mol/kg)	2.218	1.879	1.898	2.449	2.522	2.337	2.537	2.399	2.558	2.607	2.494	1.245
	Hepato-toxicity	No	No	No	No	No	No	No	No	No	No	No	No
	AMES toxicity	No	No	Yes	No	No	No	No	No	No	No	No	No
Excretion	Renal OCT substrate	No	No	No	No	No	No	No	No	No	No	No	No
Metabolism	CYP2D6 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No
	CYP2D6 substrate	No	No	No	No	No	No	No	No	No	No	No	No
Distribution	CNS	–3.74	–3.903	–3.376	–2.228	–3.96	–2.296	–4.376	–3.533	–3.743	–4.053	–3.983	–3.545
	BBB	–1.102	–1.091	–1.046	–0.939	–2.184	0.025	–1.811	–1.272	–1.847	–1.243	–1.133	–1.032
Absorption	Intestinal absorption	43.374	63.774	76.635	74.29	47.395	86.291	43.334	86.684	62.096	59.181	37.825	41.903
	Water solubility	–2.56	–1.853	–2	–3.04	–2.894	–2.497	–2.892	–3.181	–2.911	–2.967	–2.493	–3.539

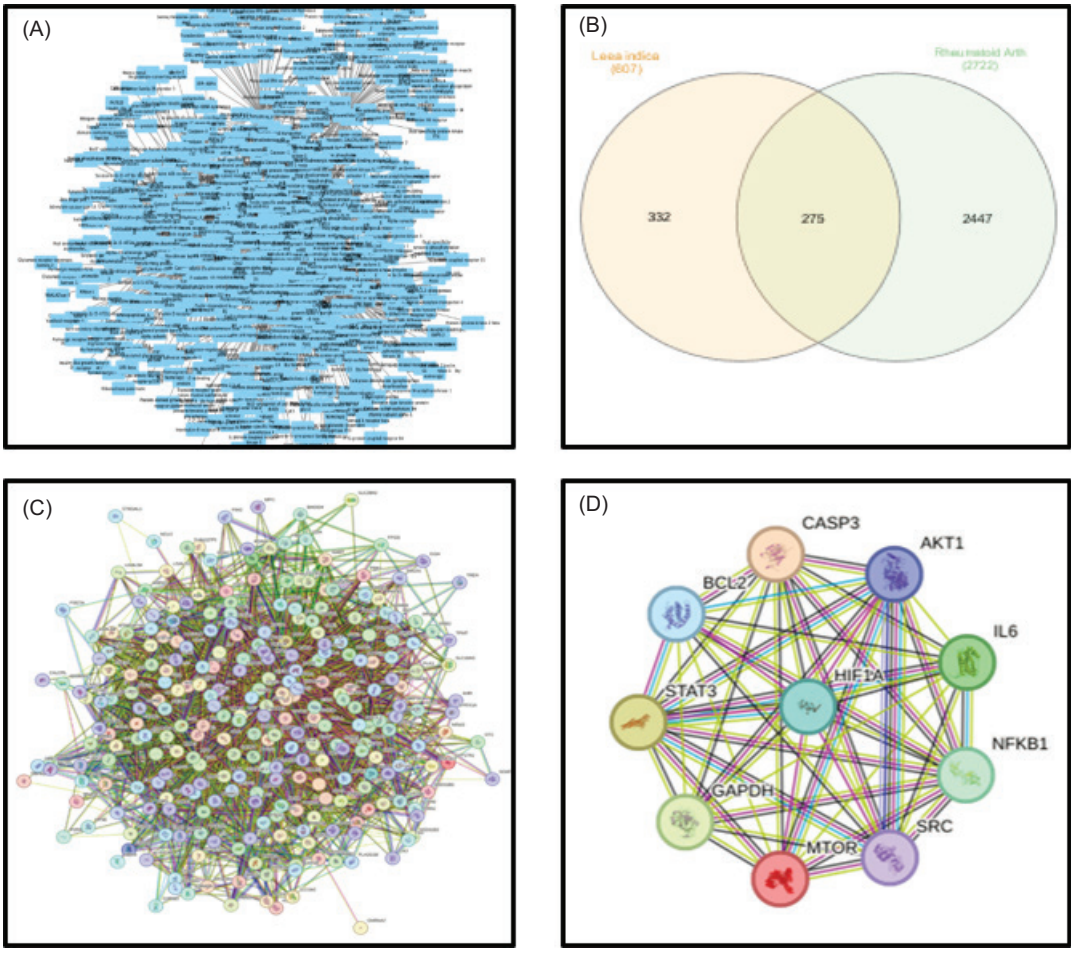

Figure 4. (A) shows the compound–target interaction network of *Leea indica* bioactives visualized using Cytoscape, illustrating multitarget connectivity with RA-related pathways. (B) presents a Venn diagram illustrating the overlap between *Leea indica* targets and RA-associated genes, identifying 275 common targets for further analysis. (C) shows the PPI network of the 275 shared targets constructed using STRING, highlighting dense protein–protein interactions relevant to RA pathophysiology. (D) presents the hub gene subnetwork of the top 10 key targets (e.g., AKT1, IL6, NFKB1, CASP3, and GAPDH) with the highest interaction degrees.

3.8. Molecular docking conformations

3.8.1. Docking conformation of 51C4-Kaempferol-3-O-arabinoside complex

The highly stable interaction indicated by the low binding energy value of −9.23 kcal/mol suggests that kaempferol-3-O-arabinoside fits well within the protein's binding pocket, as shown in Figure 5A and B. The compound's stability is enhanced by several hydrogen bonds, particularly with residues such as GLY, SER, and ARG, which likely strengthen its inhibitory or modulatory potential. The low binding energy and the combination of hydrophobic and polar contacts highlight the potential of kaempferol-3-O-arabinoside as an effective RA treatment. The mediation of anti-inflammatory effects may depend on specific interactions with residues such as GLN and CYS. The stable binding conformation of this compound highlights its therapeutic potential and supports its role in influencing important pathways associated with RA.

3.8.2. Docking conformation of 1LQB-Catechingallate complex

A steady and strong association is indicated by the binding energy of −9.04 kcal/mol for the ILQB–Catechin gallate complex, as shown in Figure 6A and B. Van der Waals forces, alkyl bonds, and traditional hydrogen bonds, specifically with the amino acid residues GLU, ARG, and ASP, all contribute to stabilizing the complex. These hydrogen bonds with GLU C:160, ARG C:167, and ASP C:190 greatly increase the binding affinity of catechin gallate. The binding interaction is further strengthened by important surrounding residues, including THR C:157, GLY C:127, LYS C:159, LYS C:196, PRO C:192, ASN C:193, ASP C:197, ASP C:187, and GLU

Table 4

Molecular Docking Scores (Binding Energies in kcal/mol) of *Leea indica* Bioactive Compounds with RA-Related Target Proteins. This table summarizes the binding affinities of six selected bioactive compounds from *Leea indica* against key RA-related proteins using molecular docking. Lower (more negative) binding energy values indicate stronger binding affinity. Notably, Kaempferol-3-O-arabinoside showed the strongest binding with GAPDH (−10.17 kcal/mol) and CASP3 (−9.23 kcal/mol), while Catechin gallate exhibited high affinity with AKT1 (−9.4 kcal/mol), suggesting their potential as lead compounds for further investigation.

Protein name	PDB ID	Ellagic acid	Catechin gallate	Epigallo-catechin	Kaempferol-3-O-arabinoside	Methyl gallate	Kaempferol
CASP3	51C4	−9.18	−7.83	−7.81	**−9.23**	−6.66	−6.4
HIF1A	1LQB	−6.21	**−9.04**	−3.6	−8.04	−6.21	−6.68
BCL2	5JSN	**−9.25**	−5.69	−6.55	−6.12	−6.68	−6.41
IL6	4CNI	**−8.1**	−4.92	−6.9	−8.01	−6.32	−7.25
GAPDH	6YND	−9.86	−6.95	−7.03	**−10.17**	−6.4	−8.27
AKT1	1UNQ	−2.64	**−9.4**	−6.0	−7.53	−6.36	−8.47
STAT3	4ZIA	−6.76	−5.87	−5.33	−6.58	−6.2	−4.73

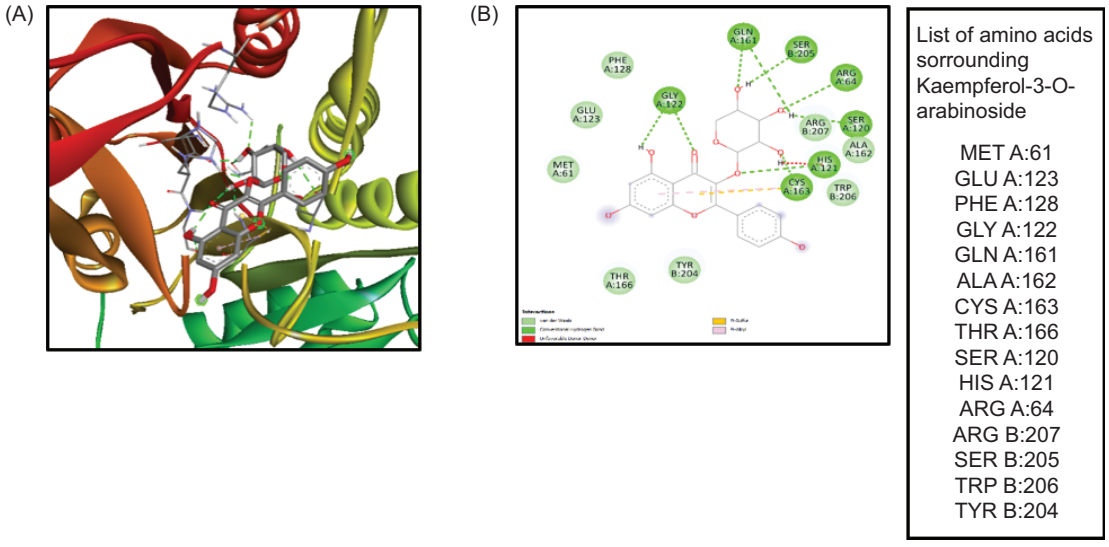

Figure 5. (A,B) Molecular docking interaction of kaempferol-3-O-arabinoside with CASP3 (PDB ID: 51C4). (A) displays the 3D binding conformation of kaempferol-3-O-arabinoside within the active site of caspase-3, showing its fit within the protein's binding pocket. (B) presents the 2D interaction diagram, highlighting multiple hydrogen bonds and hydrophobic interactions with key amino acid residues such as GLY122, SER205, ARG64, and CYS163. These interactions support the compound's strong binding affinity (−9.23 kcal/mol) and its potential role in modulating apoptotic signaling in RA.

C:186. This interaction profile highlights the therapeutic potential of catechin gallate in RA through the modulation of inflammation-related pathways.

3.8.3. Docking conformation of 5JSN-Ellagic acid complex

A strong and persistent association is indicated by the binding energy of −9.25 kcal/mol for the 5JSN–Ellagic acid complex, as shown in Figure 7A and B. Van der Waals forces, alkyl bonds, conventional hydrogen bonds with ASP, and carbon-hydrogen bonds with LEU all contribute to stabilizing the complex. Important amino acid residues surrounding ellagic acid include LEU D:115, TYR D:30, ARG D:34, MET D:42, ASP D:37, THR D:39, ARG D:43, ALA D:33, LEU D:36, LEU D:38, and LYS D:114. The overall binding affinity is strengthened by hydrogen bonding interactions with ASP D:37, carbon-hydrogen bonds with LEU D:115, and hydrophobic interactions with nearby residues. According to these results, ellagic acid may effectively interact with targets involved in inflammatory pathways, making it a viable treatment option for RA.

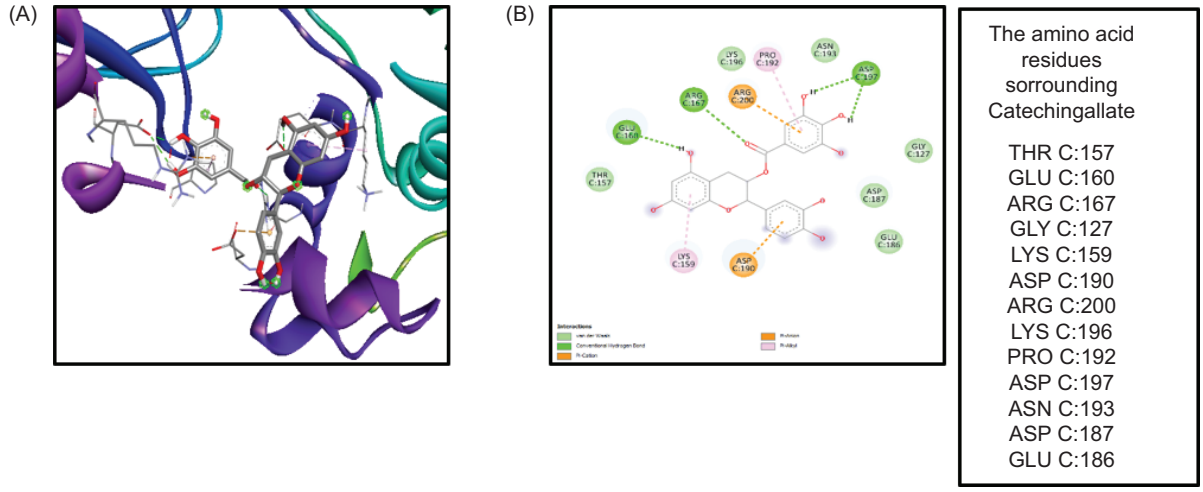

Figure 6. (A,B) Molecular docking interaction of catechin gallate with HIF1A (PDB ID: 1LQB). (A) illustrates the 3D binding pose of catechin gallate within the active site of HIF1A, showing how the molecule aligns with the protein's binding cavity. (B) depicts the 2D interaction map, highlighting hydrogen bonds and Pi–Pi stacking interactions with residues such as ASN790, ARG792, ASP804, and LYS786. These interactions support the strong binding affinity (−9.04 kcal/mol), suggesting a regulatory role of catechin gallate in hypoxia-related pathways involved in RA inflammation.

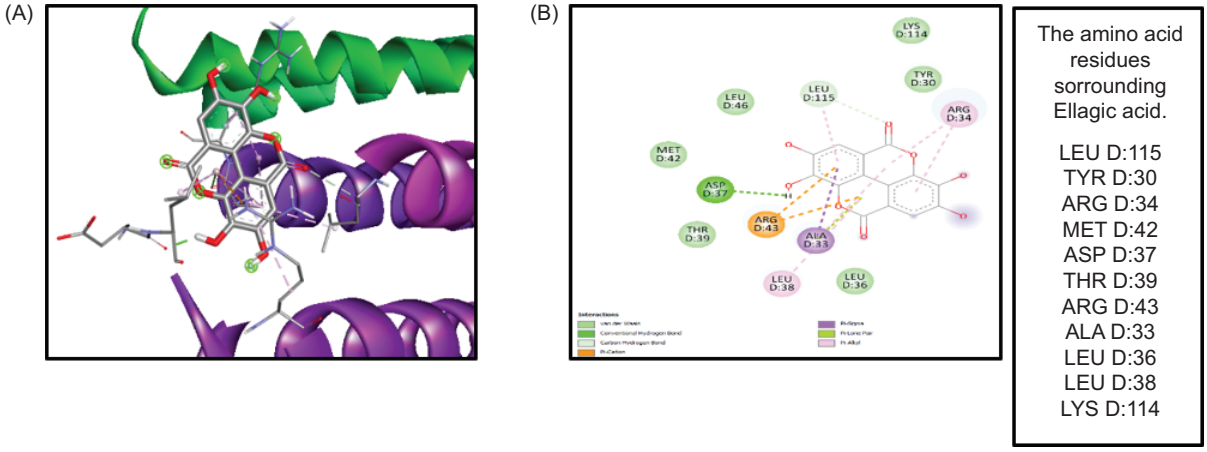

Figure 7. (A) displays the 3D conformation of ellagic acid bound within the active site of the 5JSN protein, revealing its spatial orientation and encapsulation between two helices. (B) presents the 2D interaction map, highlighting key molecular contacts such as hydrogen bonds and hydrophobic interactions with residues such as ARG D:43 and LEU D:115. Together, the figures demonstrate a stable binding configuration, offering insights into how ellagic acid may influence the structural or functional dynamics of the 5JSN protein.

3.8.4. Docking conformation of 4CNI-Ellagic acid complex

With a binding energy of −8.1 kcal/mol, the 4CNI–Ellagic acid complex, as shown in Figure 8A and B, exhibits a fairly strong interaction. Van der Waals forces, alkyl bonds, and conventional hydrogen bonds with PHE, ILE, LYS, and SER stabilize the complex. Important amino acid residues surrounding ellagic acid include SER L:171, SER L:168, ASP L:167, GLU L:105, GLU L:165, GLU L:81, ILE L:106, GLN L:166, PRO L:40, PRO L:80, PHE L:83, ALA L:84, and LYS L:39. The complex is stabilized by hydrophobic contacts from the surrounding residues, as well as by conventional hydrogen bonds formed with PHE L:83, ILE L:106, and LYS L:39. These findings suggest that ellagic acid may be capable of modulating important targets implicated in inflammation and other relevant processes, making it a potential candidate for therapeutic investigation.

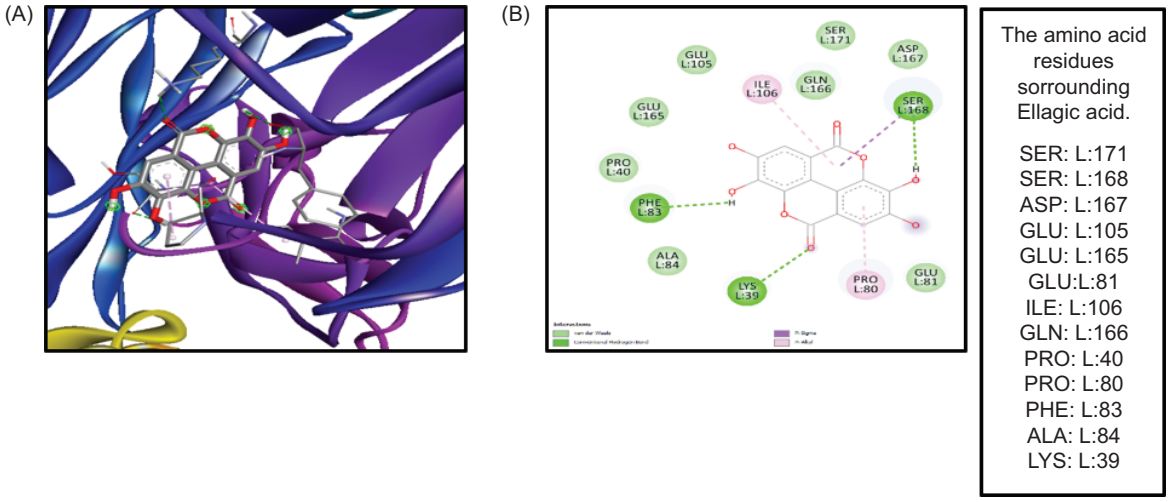

Figure 8. (A) illustrates the 3D conformation of ellagic acid nestled within the binding site of the 4CNI protein, demonstrating its spatial accommodation and surface complementarity. (B) shows the 2D interaction map of the 4CNI–Ellagic acid complex. This figure depicts the 3D docking pose of ellagic acid within the binding pocket of the 4CNI protein, demonstrating a snug fit guided by key interactions. Ellagic acid forms hydrogen bonds with residues such as SER L:168, GLN L:166, and GLU L:81, thereby enhancing binding specificity. Hydrophobic interactions with PRO L:80, PHE L:83, and ILE L:106 further stabilize the complex, suggesting a promising binding affinity.

3.8.5. Docking conformation of 6YND- Kaempferol-3-O-arabinoside complex

With a substantial binding energy of −10.17 kcal/mol, the 6YND–Kaempferol-3-O-arabinoside complex, as shown in Figure 9A and B, exhibits a very stable and favourable association. Van der Waals forces, alkyl bonds, carbon-hydrogen bonds with THR, and conventional hydrogen bonds with PRO, LEU, GLY, and ASP all contribute to stabilizing the complex. Important amino acid residues surrounding kaempferol-3-O-arabinoside include SER H:51, SER C:284, THR H:52, THR C:237, GLN A:204, GLN E:204, ASN C:287, ASN C:239, ASN H:239, ASN H:287, PRO A:236, PRO H:236, PRO E:236, LEU C:203, LEU H:203, ALA H:238, and VAL H:240. The carbon-hydrogen bonds with THR and the conventional hydrogen bonds with PRO, LEU, GLY, and ASP are essential for maintaining the stability of the interaction. These interactions demonstrate the capacity of kaempferol-3-O-arabinoside to alter important molecular pathways, thereby supporting its therapeutic potential in inflammatory and oxidative stress-related disorders.

3.8.6. Docking conformation of 1UNQ-Catechingallate complex

With a binding energy of −9.4 kcal/mol, the 1UNQ–Catechin gallate complex, as shown in Figure 10A and B, exhibits a stable and favourable association. Alkyl bonds, Van der Waals forces, and conventional hydrogen bonds, especially with ALA and GLU, all contribute to stabilizing the complex. Important amino acid residues surrounding catechin gallate include GLN A:47, GLN A:43, PRO A:42, PRO A:51, GLU A:40, TYR A:38, ALA A:50, ARG A:41, LEU A:52, and LYS A:39. The stability of the binding complex is greatly enhanced by hydrophobic contacts from surrounding residues, as well as by conventional hydrogen bonds formed with ALA and GLU. These findings suggest that catechin gallate may effectively modulate the target protein, thereby providing therapeutic benefits for inflammatory disorders such as RA.

***3.8.7.** Docking conformation of 4ZIA-Ellagic acid complex*

With a binding energy of −6.76 kcal/mol, the 4ZIA–Ellagic acid complex, as shown in Figure 11A and B, exhibits a fairly strong interaction. Van der Waals forces, alkyl bonds, particularly with LEU, and conventional hydrogen bonds with GLY all contribute to the stability of the complex. Furthermore, carbon-hydrogen bonds facilitate the binding interaction. Important amino acid residues surrounding ellagic acid include GLU D:112, GLU D:111, LEU D:115, LEU D:21, ARG D:114, THR D:118, GLN D:17, and GLN D:20. The interactions with LEU and GLY, along with hydrogen bonding with GLU and other nearby residues, improve the binding stability and specificity. These findings suggest that ellagic acid may influence important targets associated with oxidative stress and inflammation, thereby providing therapeutic benefits for diseases such as RA.

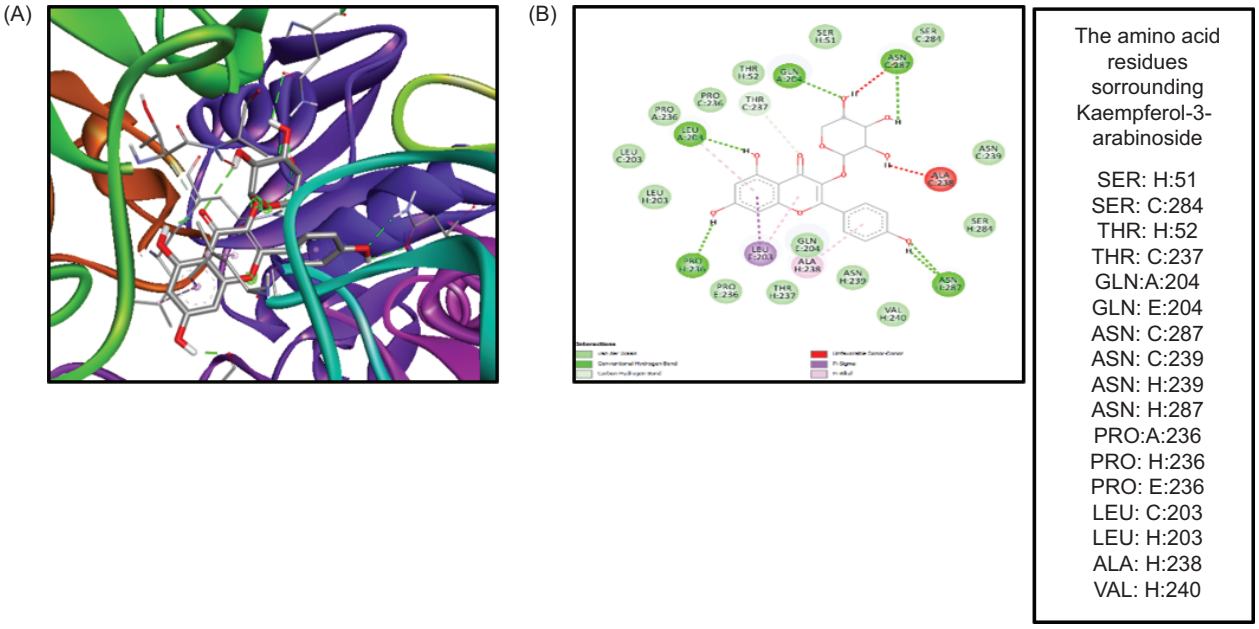

Figure 9. (A) presents the 3D binding orientation of kaempferol-3-O-arabinoside nestled within the active site of the 6YND protein. (B) shows the 2D interaction profile of the 6YND–Kaempferol-3-O-arabinoside complex, highlighting hydrogen bonds, Pi-stacking, and hydrophobic contacts. Key interactions, such as conventional hydrogen bonds and Pi–Pi stacking, contribute to the ligand's stable orientation within the binding site.

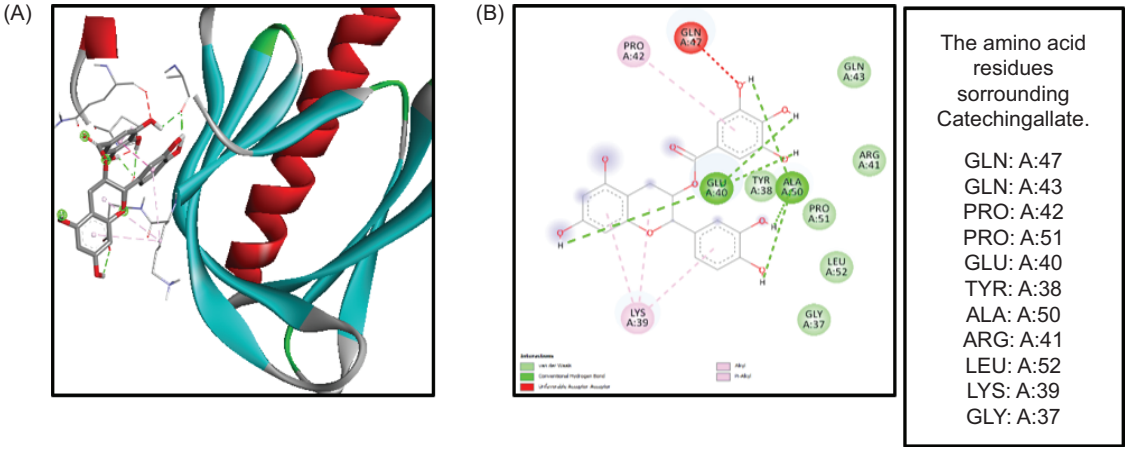

Figure 10. (A) shows the 3D interaction, and (B) shows the 2D interaction overview of the 1UNQ–Catechin gallate complex. This figure combines both the 3D binding conformation and the 2D interaction profile of catechin gallate within the active site of the 1UNQ protein. The 3D model illustrates the ligand nestled within a structured pocket surrounded by alpha helices and beta sheets, while the 2D map highlights key molecular interactions such as hydrogen bonds and hydrophobic contacts with residues such as PHE A:34 and ASN A:100. Together, these visuals emphasize a stable and specific binding mode, supporting the potential bioactivity of catechin gallate.

4. DISCUSSION

Alkaloids, flavonoids, saponins, reducing sugars, and cardiac glycosides were identified in our phytochemical screening of *Leea indica* leaves, whereas tannins, phenols, proteins, and amino acids were not detected. On the other hand, Kc and Kumar (2023) identified tannins, phenols, saponins, steroids, and glycosides as important components. The overlap in these

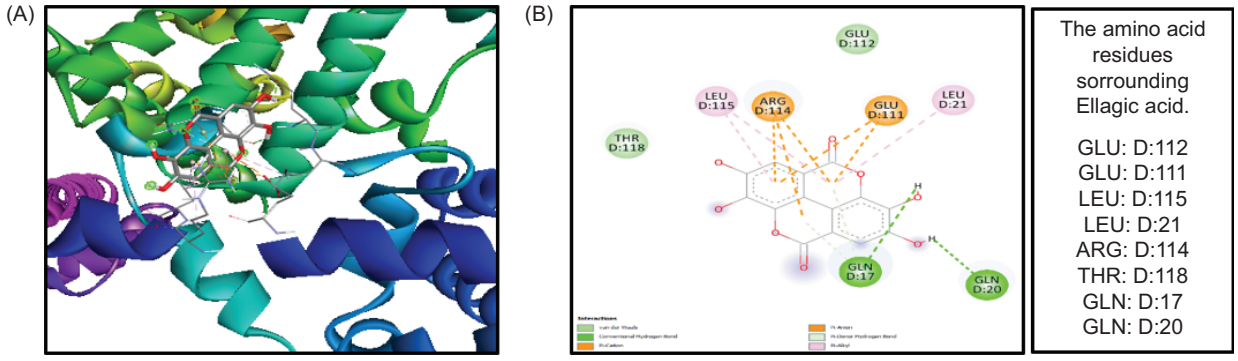

Figure 11. (A) shows the 3D interaction, and (B) presents the 2D interaction overview of the 4ZIA–Ellagic acid complex. This figure combines both the 3D docking pose and the 2D interaction map of ellagic acid bound to the 4ZIA protein. The 3D view shows the ligand embedded within the active site and surrounded by defined structural elements, while the 2D diagram highlights key interactions such as hydrogen bonding with HIS 228 and π–π stacking with TYR 241.

metabolites supports the pharmacological significance of saponins and glycosides and validates their consistency across investigations. However, our identification of alkaloids, flavonoids, and reducing sugars expands the chemical profile, indicating additional therapeutic potential. Another investigation on *Leea indica* root identified alkaloids, flavonoids, tannins, and saponins, confirming the plant's richness in a variety of secondary metabolites. This consistency across separate studies strengthens the evidence supporting its pharmacological potential (Sutrisno, Sodik and Fakih, 2025). With activity increasing from 51.02% at 100 µg/mL to 78.02% at 300 µg/mL, our phosphomolybdenum assay findings clearly demonstrated a concentration-dependent antioxidant effect. Although our extract expresses total antioxidant capacity in a different manner, it exhibited comparable effectiveness when compared with the radical scavenging assays reported for *Leea indica* leaves (DPPH 72%, ABTS 72%). The cumulative contribution of phytochemicals such as alkaloids, flavonoids, saponins, and glycosides is highlighted by the gradual increase in phosphomolybdenum activity, supporting the medicinal significance of *Leea indica* as a potential source of natural antioxidants (Karim et al., 2025).

Using a network pharmacology technique and molecular docking analysis, the current study illustrates the medicinal potential of *Leea indica* for the treatment of RA. The main objectives of this section are to interpret the relevance of the results, emphasize important discoveries, and place them within the broader context of previous research. The findings showed that a number of the bioactive components of *Leea indica* have high binding affinities for proteins linked to RA, indicating a potential role in regulating immunological responses and inflammation. Among the twelve compounds examined, methyl gallate, kaempferol, and ellagic acid exhibited the highest binding affinities toward important RA-related proteins. These results are significant because they support the multitarget modulation capability of the bioactive ingredients in *Leea indica*. The translational potential of *Leea indica* phytoconstituents is further supported by the ADMET predictions. A positive safety profile was suggested by the excellent intestinal absorption, lack of hepatotoxicity, and absence of CYP2D6 inhibition or substrate activity exhibited by the majority of the compounds. Only methyl gallate exhibited AMES toxicity, which is noteworthy and emphasizes the necessity for experimental confirmation. Although computational predictions offer valuable insights, more advanced in vitro cellular studies and in vivo investigations are required to fully assess the bioavailability, metabolic stability, and therapeutic efficacy of these compounds. These findings are consistent with the concepts of network pharmacology, which propose that herbal remedies modulate intricate disease networks through interactions with multiple biological targets (Hopkins, 2021; Zheng et al., 2022). This concept is further supported by the multiple interactions observed in the compound–target network, implying that the bioactive compounds in *Leea indica* may act cooperatively to alleviate RA symptoms. According to the docking data, ellagic acid and kaempferol-3-O-arabinoside exhibited high binding affinities toward RA-related proteins, including IL-6 and TNF-α. Both TNF-α and IL-6 are recognized mediators of inflammatory responses in RA. These results suggest that the bioactive constituents of *Leea indica* may reduce inflammation by inhibiting the activity of these cytokines, thereby alleviating joint inflammation and the immunological responses responsible for cartilage deterioration in RA patients. In particular, kaempferol is widely recognized for its anti-inflammatory properties (Imran et al., 2022), and previous research has indicated that it is effective in reducing the expression of inflammatory cytokines. Our study supports these findings

by demonstrating that kaempferol-3-O-arabinoside has a high binding affinity toward TNF-α, suggesting its potential to inhibit TNF-α activity in RA. The network pharmacology analysis also identified numerous novel targets, including fibroblast-like synoviocytes (FLS) and protein tyrosine phosphatase non-receptor type 22 (PTPN22), both of which are essential in the pathophysiology of RA. Dysfunction of PTPN22, a crucial regulator of immunological tolerance, has been associated with increased susceptibility to autoimmune diseases, including RA (Stanford & Bottini, 2021). The identification of *Leea indica* compounds targeting PTPN22 creates new opportunities for potential therapeutic intervention, particularly in refractory RA, where conventional therapies may be ineffective. Furthermore, FLS are widely known to contribute to synovial hyperplasia and joint deterioration (Nygaard & Firestein, 2020; Bottini & Firestein, 2021). By targeting FLS, *Leea indica* may offer an additional therapeutic strategy to delay the progression of joint degeneration in RA patients. Although in silico methods such as molecular docking and network pharmacology provide valuable insights into potential compound–target interactions, experimental validation is essential to confirm their biological significance. In the present study, the predicted bioactivity of *Leea indica* was preliminarily supported through phytochemical screening and antioxidant and anti-inflammatory assays. These findings further support the potential of the plant as a treatment for rheumatoid arthritis. However, additional research using advanced in vitro cellular models and in vivo systems is required to comprehensively evaluate the pharmacological mechanisms, therapeutic efficacy, and safety profile of the identified compounds.

The current study evaluates the anti-rheumatoid arthritis potential of bioactive compounds from *Leea indica* using a comprehensive in silico framework that includes target prediction, network pharmacology, molecular docking, and SWISSADME-guided compound screening. Target selection required a thorough evaluation of the specificity of associations identified using the term "rheumatoid arthritis." Despite the possibility of inconsistent results from such searches, we aimed to enhance disease relevance by removing duplicates following UniProt mapping and retaining only high-confidence associations (DisGeNET score > 0.1). This filtering process reduced noise and ensured that the final target set represented carefully selected and physiologically significant associations. However, we acknowledge that future research should employ more stringent evidence-level criteria or curated RA-specific datasets to further improve specificity and reproducibility, as keyword-based retrieval may capture targets with varying levels of relevance.

While the bioactive compounds of *Leea indica* showed strong in silico interactions with RA-related proteins, these findings must be interpreted cautiously. Docking scores do not account for pharmacokinetic factors such as bioavailability, metabolic stability, or target accessibility in vivo. Therefore, these results should be viewed as hypothesis-generating and as providing leads for further experimental validation. The SWISSADME study enabled the selection of twelve phytocompounds with favourable physicochemical and drug-like characteristics. Among them, polyphenols with well-established anti-inflammatory and antioxidant properties, which are crucial in the pathophysiology of RA, such as kaempferol, gallic acid, ellagic acid, and catechin derivatives, stood out.

The compound–target interaction network highlights the multitarget therapeutic potential of *Leea indica*. Multiple interactions with RA-associated targets were demonstrated by compounds such as gallic acid, ellagic acid, and kaempferol, suggesting their ability to influence a variety of biochemical processes. This supports a systems-level therapeutic strategy, which is especially beneficial in complex, multifactorial disorders such as RA, where monotarget medications frequently fail. The rich target connectivity identified through Cytoscape demonstrates the synergistic potential of various bioactive compounds and highlights the comprehensive nature of phytomedicine in reducing inflammation and re-establishing immunological balance. According to the Venn diagram analysis, *Leea indica* compounds and RA-associated genes share 275 targets, further supporting the therapeutic potential of these phytoconstituents. PPI network analysis and pathway enrichment also revealed important hub proteins, including AKT1, IL6, NFKB1, CASP3, and GAPDH, which are crucial regulators in apoptotic signaling and immune-inflammatory cascades. These hub targets represent important nodes through which *Leea indica* compounds may exert immunomodulatory and systemic anti-inflammatory effects. Molecular docking studies provided atomic-level information on the binding efficiency of specific compounds with important RA-related proteins. Notably, kaempferol-3-O-arabinoside exhibited the highest binding affinities, particularly with GAPDH (–10.17 kcal/mol) and CASP3 (–9.23 kcal/mol), which were stabilized through hydrophobic interactions and conventional hydrogen bonds. These findings suggest the ability of the compound to modulate apoptotic and glycolytic pathways, both of which are associated with the pathophysiology of RA. Ellagic acid demonstrated a broad-spectrum anti-inflammatory profile through its consistently high binding affinities across several targets, including BCL2 (–9.25 kcal/mol), IL6 (–8.1 kcal/mol), and STAT3 (–6.76 kcal/mol). The interaction with STAT3 is particularly significant because this protein plays an essential role in cytokine signaling and RA progression. Catechin gallate also exhibited significant binding affinities with AKT1 (–9.4 kcal/mol) and

HIF1A (–9.04 kcal/mol), suggesting its possible involvement in regulating hypoxia-driven inflammation, a hallmark of the rheumatoid synovial milieu. The absence of redocking and RMSD validation means that docking reliability could not be quantitatively assessed. Future studies should incorporate these procedures to confirm the accuracy of the predicted binding poses. In addition to confirming the computationally predicted target-binding efficiency of *Leea indica* compounds, these findings also suggest possible molecular mechanisms, including the inhibition of transcription factors (STAT3, NF-κB), regulation of apoptosis (CASP3, BCL2), and suppression of pro-inflammatory cytokines (IL-17, TNF-α).

The pathophysiology of RA is largely mediated by the well-recognized NF-κB, TNF, and IL-17 pathways, which contribute to chronic inflammation, synovial hyperplasia, and joint damage (Burmester & Pope, 2022; McInnes & Schett, 2021). TNF signaling promotes synovial inflammation and cartilage degradation, NF-κB regulates the production of pro-inflammatory cytokines and adhesion molecules, and IL-17 enhances immune responses by recruiting neutrophils and activating matrix metalloproteinases. Several phytocompounds identified in this investigation showed docking interactions with proteins upstream or downstream of these pathways, indicating possible mechanistic intervention. For example, compounds that interact with NF-κB regulators may reduce the transcriptional activation of inflammatory mediators, whereas those targeting TNF-related nodes may suppress cytokine signaling. Consequently, the network-based identification of these pathways, together with the docking results, suggests potential mechanisms through which phytocompounds from *Leea indica* may influence the pathophysiology of RA. Although network pharmacology and molecular docking have been widely applied to natural compounds in RA research, most studies either focus on a single phytochemical or fail to integrate multiple bioactive compounds. Our study provides a novel evaluation of the multitarget binding profile of *Leea indica*, a plant with limited prior mechanistic investigation in RA. Previous studies on plants such as *Curcuma longa* (curcumin), *Camellia sinensis* (catechins), and *Moringa oleifera* (isothiocyanates) have demonstrated anti-RA efficacy using network pharmacology and docking approaches (Zhang et al., 2022; Li et al., 2021). However, the phytochemical composition of *Leea indica* is distinct. In particular, kaempferol-3-O-arabinoside, ellagic acid, and catechin gallate exhibited significant binding affinities toward CASP3, GAPDH, IL-6, and AKT1. This comparative perspective highlights the originality of our work and identifies novel bioactive candidates for RA research. By positioning *Leea indica* within the broader context of phytopharmaceutical research, this study advances current knowledge and generates testable hypotheses for experimental validation, including cytokine suppression assays (IL-6, TNF-α), apoptosis modulation studies (CASP3, BCL2), and synoviocyte culture models to evaluate anti-inflammatory activity. Overall, this comprehensive in silico approach supports the therapeutic potential of *Leea indica* as a natural, multicomponent treatment for RA.

The bioactive profile of the plant provides potential opportunities for the development of therapeutics targeting computationally identified molecules, which may address the complex nature of the disease and potentially overcome the limitations of conventional treatments. Nevertheless, further experimental validation through in vitro and in vivo investigations is necessary to confirm these interactions and demonstrate pharmacodynamic efficacy and safety.

5. LIMITATIONS AND FUTURE DIRECTIONS

Although this study integrates in silico analysis with preliminary experimental investigations, several limitations remain. Network pharmacology and molecular docking provide predictive insights into compound–target interactions but cannot independently confirm therapeutic efficacy. While phytochemical screening and antioxidant and anti-inflammatory assays demonstrated the presence of bioactive compounds and biological activity in *Leea indica*, these assays represent only preliminary validation. Future studies should include detailed cell-based assays, such as cytokine inhibition assays and experiments using fibroblast-like synoviocytes, followed by in vivo rheumatoid arthritis models to confirm pharmacological effects. Additionally, factors such as bioavailability, metabolic stability, and target accessibility should be evaluated to better understand the therapeutic potential of the compounds prior to clinical translation.

6. CONCLUSION

This study investigated the therapeutic potential of *Leea indica* against rheumatoid arthritis using an integrative approach that combined network pharmacology, molecular docking, and preliminary experimental validation. Computational analyses revealed several bioactive compounds capable of interacting with important RA-associated targets such as AKT1, CASP3, IL6, STAT3, and GAPDH, suggesting that the phytoconstituents of *Leea indica* may exert therapeutic effects through a multitarget regulatory mechanism. Network pharmacology analysis also identified the involvement of important inflammatory signaling pathways, including NF-κB, TNF, and IL-17, which are crucial in the pathophysiology of rheumatoid arthritis. Molecular docking studies demonstrated strong binding affinities between several phytocompounds,

particularly kaempferol-3-O-arabinoside, ellagic acid, and catechin gallate, and these RA-related proteins, indicating their potential role in regulating inflammatory and apoptotic processes. Phytochemical screening revealed the presence of several biologically active secondary metabolites, including flavonoids, alkaloids, saponins, glycosides, and reducing sugars, which are commonly associated with antioxidant and anti-inflammatory properties. These preliminary experimental findings further supported the computational predictions. Additionally, the phosphomolybdenum assay demonstrated that the *Leea indica* extract exhibited significant antioxidant activity in a concentration-dependent manner, suggesting its potential to combat oxidative stress, which is a major factor in the progression of rheumatoid arthritis. Significant anti-inflammatory activity of the extract was also demonstrated by the egg albumin denaturation inhibition assay; at higher concentrations, the inhibitory effects were comparable to those of the standard drug indomethacin. Collectively, these findings indicate that *Leea indica* is a potentially valuable natural source of bioactive compounds capable of modulating inflammatory signaling pathways and oxidative stress in rheumatoid arthritis. However, further research using advanced in vitro cellular models, mechanistic studies, and in vivo rheumatoid arthritis models is required to validate the pharmacological mechanisms, therapeutic efficacy, and safety profile of these compounds before their potential clinical application can be established.

ETHICAL APPROVAL

This research is based on computational methods and does not involve human or animal subjects; therefore, ethical approval is not required.

MANDATORY DISCLOSURE ON USE OF ARTIFICIAL INTELLIGENCE

None.

AUTHORS CONTRIBUTIONS

Conceptualization: M.A,R., V.R.V.R., Y.B.C., A.K.P.; Writing original draft- Mersiha Abdul Rahim, Vinith R.V.R.; Editing: Y.B.C.; Review and Editing: A.K.P.

COMPETING INTEREST

Authors have declared that no competing interests exist.

CONSENT

This study does not involve human participants, and therefore patient consent is not applicable.

ACKNOWLEDGEMENT

The authors thank the BSACIST management for providing necessary research support.

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