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RESEARCH ARTICLE

INTEGRATED NETWORK PHARMACOLOGY AND MOLECULAR DOCKING BASED IDENTIFICATION OF ANTI-RHEUMATOID ARTHRITIS POTENTIAL OF *LANTANA CAMARA*

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Abstract

Aim and Objectives: This study aimed to elucidate the potential anti-rheumatoid arthritis mechanisms of *Lantana camara* L. using an integrated approach combining LC–HRMS, network pharmacology, and molecular docking.
Methods: From the methanolic extract of *L. camara*, 83 compounds were identified. Among these, 17 met the drug likeness criteria and were selected for further investigation. Target prediction and disease gene integration revealed 15 overlapping targets associated with RA. Protein-protein interaction (PPI) network analysis and functional enrichment analysis were performed to identify hub targets and key pathways. Molecular docking was then conducted to evaluate binding affinities of selected compounds.
Results: PPI network analysis identified key hub targets such as IL6, APP, MMP2, ITGB2, PLAU, MMP14, TTR, and MPO. Functional enrichment analysis showed significant involvement in the IL-17 signalling pathway. Molecular docking revealed that Compound 19 had the strongest binding affinity to MMP2 (−9.069 kcal/mol), outperforming aspirin, and exhibited binding energy comparable to prednisolone against IL-6 with a greater number of hydrogen bond interactions. Compound 12 also showed notable interactions, albeit with lower affinity.
Conclusion: Compound 19 emerged as a promising multi-target candidate with potential anti-RA activity through modulation of key inflammatory mediators, including IL-6, MMP2, and MPO. These findings support the traditional use of *L. camara* in rheumatism and highlight its potential as a source of novel anti-inflammatory agents. Further experimental validation is needed. The docking protocol was validated by redocking the native ligand (RMSD < 2.0 Å). Although these *in silico* findings are promising, experimental validation using *in vitro* enzyme inhibition assays and *in vivo* RA animal models is required to confirm the therapeutic potential of Compound 19.
Keywords: *Lantana camara*, molecular docking, natural products, network pharmacology, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease according to the Global Burden of Disease Study 2021, the global prevalence of RA is approximately 0.5–1.0%, with higher incidence in women and in high-income countries[1] characterized by persistent synovial inflamemation, progressive joint destruction, and various systemic complications[2]. Recent epidemio-logical evidence indicates that the incidence and prevalence of RA continue to evolve, posing a significant burden on global healthcare systems[3]. The etiology of RA involves a complex interplay between genetic susceptibility, environmental factors, and dysregulation of both adaptive and innate immune responses[2]. The pathogenesis of RA is driven by multiple inflammatory mediators, particularly pro-inflammatory cytokines that sustain the chronic inflammatory cycle[4]. Key cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-17 (IL-17), are overproduced by synovial cells, macrophages, T lymphocytes, and fibroblast like synoviocytes (FLS), thereby amplifying synovial inflammation and joint damage[4,5]. Understanding the role of these cytokines has led to the development of targeted therapeutic strategies[5].

In addition to cytokine dysregulation, autophagy and apoptosis play crucial roles in RA pathophysiology. IL-17 has been shown to induce mitochondrial dysfunction and autophagosome formation in FLS, contributing to resistance against apoptosis[6,]. Furthermore, apoptosis signal-regulating kinase 1 (ASK1) has been reported to regulate inflammatory signalling pathways and cellular responses in RA[7]. These findings highlight the intricate relationship between mitochondrial dysfunction, autophagy, and persistent inflammation in RA. B cells and T cells are central players in RA pathogenesis. B cells contribute through the production of auto antibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), as well as antigen presentation and cytokine secretion. $CD4^+$ T cells differentiate into functional subsets, including Th1, Th17, and regulatory T cells (Treg). Among these, Th17 cells are recognized as key drivers of synovial inflammation and bone erosion, whereas impaired Treg function results in an imbalance between pro-inflammatory and anti-inflammatory responses[5].

Despite the availability of various therapeutic approaches, RA management still faces several challenges, including high treatment costs, adverse effects, and limitations associated with biologic agents. For instance, clinical and imaging evidence from biologic therapies such as golimumab has provided insights into treatment responses, yet these therapies remain constrained by safety and accessibility issues[8]. Therefore, the exploration of alternative therapeutic agents that is safer, more effective, and accessible remains a critical need.

Natural products have emerged as a promising source for novel drug discovery. *Lantana camara* is a tropical plant belonging to the *Verbenaceae* family, native to the Americas and widely distributed in tropical and subtropical regions[9,10]. Although it is often considered an invasive and toxic weed with ecological impacts[9,11,12], it possesses significant ethno medicinal value. In Indonesia, this plant is traditionally used to treat various conditions, including wounds, abscesses, eczema, malaria, tumours, and rheumatism[13].

Globally, *L. camara* has been reported to exhibit a wide spectrum of pharmacological activities, including antibacterial, anti-inflammatory, anticancer, ant malarial, antiviral, and hepatoprotective effects[14]. Its traditional use in malaria endemic regions has also been documented, particularly for leaf and root decoctions[15,16]. Moreover, previous studies have demonstrated its neuro pharmacological potential, including anticonvulsant and anxiolytic effects mediated through modulation of the GABAergic system and oxidative stress pathways[17,18]. However, despite these extensive bioactivities, the molecular mechanisms of bioactive compounds from *L. camara*, particularly methanolic extracts, in the context of RA remain insufficiently explored.

To address the complexity of multi-target interactions in disease systems, Network Pharmacology has emerged as a powerful paradigm in drug discovery[19]. This approach enables the systematic analysis of interactions among bioactive compounds, target proteins, and disease related signalling pathways. Typically, network pharmacology involves compound identification, target prediction, disease gene collection from databases such as GeneCards and OMIM, protein –protein interaction (PPI) network construction using STRING, and functional enrichment analysis through Gene Ontology (GO) and KEGG pathways. The application of this approach has been demonstrated in various studies, including investigations into molecular mechanisms of disease treatment[20].

To further validate compound target interactions, molecular docking is widely employed to predict binding affinity and interaction stability between ligands and proteins[20]. Lower binding energy values indicate stronger and more stable interactions. Docking results are subsequently visualized to analyze hydrogen bonds, hydrophobic interactions, and other key interactions at the active site. The integration of network pharmacology and molecular docking has been proven to be an effective strategy for identifying potential drug candidate's from natural products[19-21].

Therefore, this study aims to identify bioactive compounds from the methanolic extract of *L. camara* with potential therapeutic effects against rheumatoid arthritis through an integrated approach combining network pharmacology and molecular docking. The findings of this study are expected to provide a scientific basis for the development of safer and more effective RA therapies derived from natural products.

MATERIALS AND METHODS

LC-HRMS analysis and drug-likeness prediction

LC-HRMS was used as a powerful tool for qualitative analysis to characterize the chemical components of *L. camara*[22]. Drug likeness properties of the identified compounds were evaluated using the MolSoft web server (*https://www.molsoft.com*). A threshold of drug-likeness score>0.18 was applied to select compounds with more favorable drug-like characteristics for subsequent analysis. Drug likeness properties of each compound were evaluated using the Swiss ADME web server (*http://www.swissadme.ch*)[23]. The assessment was conducted based on Lipinski's Rule of five, which includes molecular weight ≤500 Da, hydrogen bond donors ≤ 5, hydrogen bond acceptors ≤ 10, and a log P value ≤ 5. Compounds violating more than one of these criteria were excluded from further analysis. The SMILES codes of each compound were submitted to the web server to obtain the corresponding drug-likeness properties.

Gene identification associated with rheumatoid arthritis

Target prediction of compounds identified from *L. camara* analysis was performed using SwissTarget Prediction (*https://www.swisstargetprediction.ch*)[23] and the Similarity Ensemble Approach (SEA) (*https://sea.bkslab.org*) database using the input SMILE code of each compound[24] database by inputting the SMILES code of each compound. Potential genes associated with rheumatoid arthritis (RA) were retrieved from Online Mendelian Inheritance in Man OMIM (*https://www.omim.org*)[25] and GeneCard (*https://www.genecards.org*)[26].

Subsequently, the predicted targets of the compounds and disease-related genes were filtered to remove duplicates and then integrated. The overlapping targets between compounds and RA-associated genes were identified and visualized using a Venn diagram generated by the Bioinformatics and Evolutionary Genomics Venn tool.

Protein–Protein interaction network analysis

A protein–protein interaction (PPI) network was constructed to evaluate the interactions among potential target genes, including co-expression, gene fusion, neighbourhood, and co-localization patterns[27]. The list of potential target genes was submitted to the STRING database (*https://string-db.org*), with *Homo sapiens* selected as the target organism. In the constructed network, each node represents a protein, while each edge indicates a functional association between proteins. The interaction data obtained from STRING were subsequently imported into Cytoscape for network visualization and topological analysis of the potential target genes.

Construction of compound target network

A compound target interaction network was constructed using Cytoscape (version 3.10.4) to elucidate the complex relationships between *L. camara* derived compounds and RA associated target genes[28]. The active compounds and their corresponding target genes were integrated and visualized through network analysis. In this network, each node represents either a bioactive compound or a target gene, while the edges denote the interactions between compounds and their associated targets. Furthermore, network topological parameters, including degree centrality and between centrality, were analyzed to identify key compounds and core target genes.

GO and KEGG enrichment analysis

Gene Ontology (GO) enrichment analysis was performed using the ShinyGO platform (version 0.85) to evaluate the biological processes[29], cellular components, and molecular functions associated with the predicted target proteins. Furthermore, pathway enrichment analysis was conducted based on the Kyoto Encyclopaedia of Genes and Genomes (KEGG) database[30] to identify the key signalling pathways and metabolic processes potentially modulated by the *L. camara* derived compounds in relation to rheumatoid arthritis (RA). The significantly enriched pathways were subsequently considered as the putative mechanisms of action underlying the therapeutic effects of the compounds.

Molecular docking

Molecular docking simulations were performed to investigate the binding interactions between selected bioactive compounds and target proteins. The three dimensional (3D) crystal structures of interleukin-6 (IL-6; PDB ID: 1N26), matrix metalloproteinase-2 (MMP-2; PDB ID: 8H78), and myeloperoxidase (MPO; PDB ID: 6WY0) were retrieved from the Protein Data Bank (PDB) (*https://www.rcsb.org*). The two dimensional (2D) structures of *L. camara* derived compounds identified through LC-HRMS analysis were converted into 3D conformations using Chem3D, followed by energy minimization to obtain stable structures. Protein and ligand preparation, including the removal of water molecules, addition of polar hydrogen atoms, and assignment of appropriate charges, were conducted using AutoDock Tools.

Docking simulations were carried out using AutoDock Vina to predict the binding affinity between ligands and target proteins. The grid box parameters were defined to encompass the active binding site of each protein. Binding affinities were expressed in kcal/mol, and the most favourable binding conformations were selected based on the lowest binding energy values. The docking poses and protein ligand interactions were subsequently visualized and analyzed using PyMOL and Discovery Studio Visualizer, following previously reported protocols[31,32].

Docking protocol validation and Grid Box parameters

To validate the docking protocol, each native ligand was extracted from its crystal structure and redocked into the same binding site, and the root-mean-square deviation (RMSD) between the predicted and crystallographic poses was calculated, where an RMSD value <2.0 Å was considered acceptable for reliable docking[33]. Molecular docking was performed using AutoDock Vina with the following grid box coordinates: for IL-6 (PDB ID: 1N26, ligand: predni-solone) center_x=16.471, center_y=48.983, center_ z=82.154, size_x=30 Å, size_y=24 Å, size_z=28 Å, exhaustiveness=8; for MMP2 (PDB ID: 8H78, ligand: aspirin) center_x=28.297, center_y=25.241, center_z=–8.419, size_x=22 Å, size_y=28 Å, size_z=18 Å, exhaustiveness=8; and for MPO (PDB ID: 6WY0, ligand: UFA) center_x=123.0, center_y=94.5, center_z=34.5, size _x=18 Å, size_y=18 Å, size_z=18 Å, exhaustiveness=8.

Statistical analysis

All computational analyses were performed using validated bioinformatics platforms and molecular docking software. Network pharmacology data, including target prediction and protein–protein interaction (PPI) network construction, were analyzed using built-in algorithms of the respective databases (STRING, Cytoscape) without additional parametric statistical tests, as these analyses are deterministic based on curated datasets. Molecular docking was performed in triplicate, and binding energies are presented as mean values. Enrichment analysis was evaluated using Fisher's exact test with FDR correction, and statistical significance was set at $p<0.05$.

RESULTS

LC-HRMS and drug-likeness analysis

LC–MS analysis was performed to identify the chemical constituents present in the methanolic extract of *L. camara*. Based on comprehensive data interpretation, including molecular formula determination, fragment ion analysis, and structural elucidation using scientific literature and public databases, a total of 83 compounds were successfully identified. The drug-likeness properties of the identified compounds were subsequently evaluated using the MolSoft platform.

Among the 83 compounds, 66 compounds with drug-likeness scores < 0.18 were excluded from further analysis. The remaining 17 compounds were selected for subsequent pharmacokinetic evaluation. Further screening was conducted using the Swiss ADME platform based on Lipinski's Rule of Five, including molecular weight, hydrogen bond donors and acceptors, and lipophilicity (log P). This evaluation aimed to assess the oral bioavailability and drug-likeness potential of the compounds.

Target identification and PPI network

A total of 792 potential targets associated with *L. camara* compounds were predicted using Swiss Target Prediction and the Similarity Ensemble Approach (SEA) database. Meanwhile, 78 RA related target genes were retrieved from the Online Mendelian Inheritance in Man (OMIM) and GeneCards databases. Common targets between *L. camara* derived compounds and RA associated genes were identified using Venn diagram analysis. A total of 15 overlapping genes were obtained and considered as potential therapeutic targets. These common targets included IL6, MMP2, APP, PIK3CG, TTR, MAPT, MPO, PLAU, IL6ST, ITGB2, MMP14, ITGAV, PTPN22, HTT, and ASAH1. These genes are considered to play crucial roles in mediating the interactions between bioactive compounds and disease-related pathways, thereby contributing to therapeutic effects of *L. camara* against RA at the molecular level. The blue region represents 778 compound related targets, while the yellow region represents 63 RA-related targets. The intersection area indicates 15 common targets shared between the two datasets. The 15 common targets were imported into the STRING database to construct a protein–protein interaction (PPI) network. The resulting network was subsequently visualized and analyzed using Cytoscape version 3.10.2. The PPI network consisted of 15 nodes and 28 edges, indicating a moderate level of interaction among the target proteins (Figure 1). Proteins with a higher number of interactions were considered to play more central roles in the network and may serve as key targets in the therapeutic mechanism of *L. camara* against rheumatoid arthritis. The CytoHubba plugin was utilized to identify core targets based on topological parameters, including degree, closeness, and between's centrality. The analysis consistently identified IL6, APP, MMP2, ITGB2, PLAU, MMP14, TTR, and MPO as key hub targets.

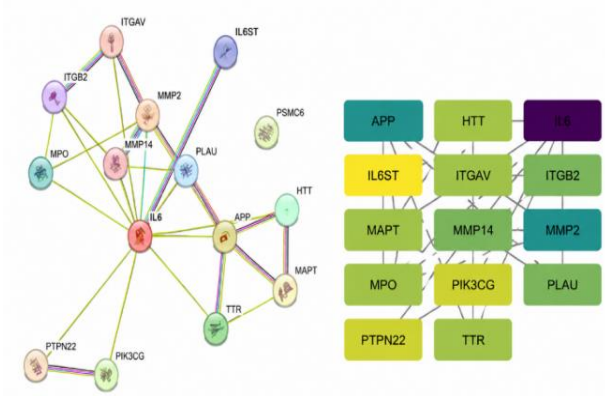

Figure 1: Protein–protein interaction network of overlapping targets.

GO and KEGG enrichment analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed using the ShinyGO platform to investigate the functional roles and signalling pathways associated with the identified common targets. A total of 15 overlapping targets between *L. camara* L. compounds and rheumatoid arthritis (RA) were analyzed. Enrichment results with a false discovery rate (FDR) or adjusted p value <0.05 were considered statistically significant. The top enriched GO terms were categorized into three domains: biological process (BP), cellular component (CC), and molecular function (MF) (Figure 2). In the BP category, the most significantly enriched term was Reg. of cell adhesion (Figure 2a). In the CC category, Interleukin-6 receptor complex showed the highest enrichment (Figure 2b). Meanwhile, in the MF category, Interleukin-6 receptor binding was identified as the most significant term (Figure 2c). KEGG pathway enrichment analysis demonstrated that the identified targets were significantly associated with multiple signalling pathways implicated in the pathogenesis of rheumatoid arthritis (Figure 2d).

Among these, the IL-17 signalling pathway exhibited the strongest enrichment. Notably, IL-6 was found to be highly upregulated, indicating its critical function as a key inflammatory mediator within these pathways. A more detailed examination of the KEGG rheumatoid arthritis pathway (hsa05323) shows a complex web of molecular interactions, beginning with antigen presenting cells such as dendritic cells that activate T cells, leading to the production of pro-inflammatory cytokines including IFNγ, IL-6, IL-17, IL-1β, IL-23, and IL-2. These cytokines collectively drive synovial inflammation, facilitate Th1 and Th17 cell differentiation, and promote osteoclastogenesis along with the release of matrix metalloproteinases (MMPs), ultimoately resulting in cartilage breakdown and bone erosion. The pathway also includes a broad spectrum of other interleukins ranging from IL-4 to IL-38, many of which have context dependent roles in either worsening or alleviating inflammation.

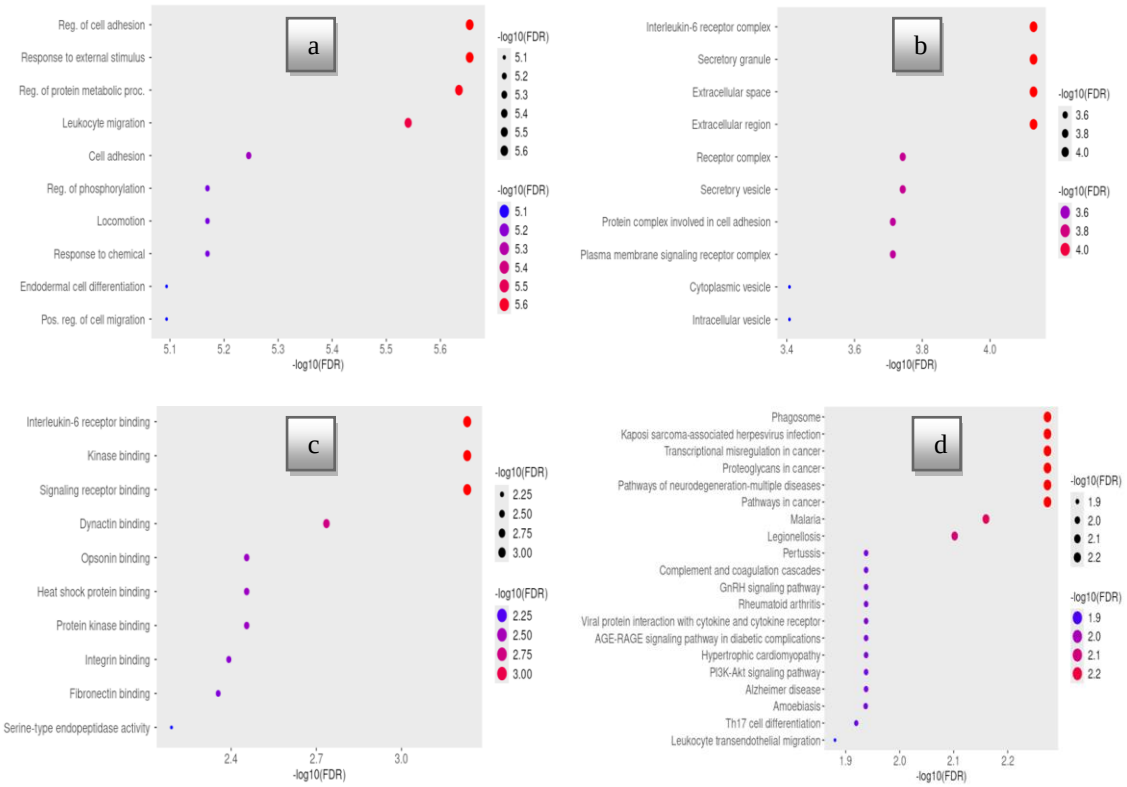

Figure 2: GO and KEGG enrichment analysis. (a) Biological process, (b) cellular component, (c) molecular function, and (d) KEGG pathway analysis.

For example, IL-18, IL-21, IL-22, and IL-33 contribute to chronic inflammation and tissue remodelling, whereas IL-4 and IL-10 may exert anti-inflammatory effects under specific conditions. The KEGG framework emphasizes the redundancy and cross-talk inherent in the cytokine network, illustrating how diverse signalling pathways contribute to the persistence and severity of the disease. Beyond the well-known TNF-α, IL-6, and IL-17 axes, KEGG analysis reveals additional potential therapeutic targets and supports the need for multi-targeted or personalized approaches in treating rheumatoid arthritis. Furthermore, integrating KEGG pathway analysis with the protein–protein interaction (PPI) network revealed that key targets such as IL-6, MMP2, and MPO are involved in several signalling pathways. These targets may act as essential mediators in the therapeutic mechanism of *L. camara* against RA.

Molecular docking analysis

All 11 compounds that passed both drug likeness (score >0.18) and Lipinski's Rule of Five were initially subjected to molecular docking against IL-6, MMP2, and MPO. Based on the preliminary docking results, Compounds 12 and 19 consistently produced the lowest binding energies and the highest number of hydrogen bond interactions with key active site residues across all three targets. Specifically, Compound 19 showed the strongest binding to MMP2 (–9.069 kcal/mol) and formed five hydrogen bonds with IL-6, while Compound 12 exhibited strong binding to MMP2 (–8.608 kcal/mol) and MPO (–7.607 kcal/mol). In contrast, the remaining nine compounds showed consistently weaker binding profiles (e.g., binding energies above –8.0 kcal/mol for MMP2 and fewer than two hydrogen bonds per target). Therefore, only Compounds 12 and 19 were selected for detailed interaction analysis and visualization, which is a standard practice in network pharmacology studies to focus on the most promising candidates[19]. As comparators, different positive controls and native ligands were used for each target: prednosolone for IL-6, aspirin for MMP2, and native ligand UFA for MPO. The docking conformation of the moist promising target (MMP2) is depicted in (Figure 3). On the IL-6 target (PDB ID: 1N26), Compound 19 produced more hydrogen bond interactions with residues Ser106 (3.21 Å), Ser224 (2.41 Å), Gln158 (2.80 Å), Ser156 (2.61 and 3.07 Å), and Glu114 (2.66 Å), as compared to the positive control prednisolone which had hydrogen bonds only with Ser106 (2.80 Å). The binding energy of Compound 19 (-6.269 kcal/mol) was comparable to that of prednisolone (-6.405 kcal/ mol), while Compound 12 exhibited a binding energy of -6.280 kcal/mol with hydrogen bonds to Lys105 (3.14 Å), Gln196 (3.03 Å), Ile194 (2.01 Å), and Ser101 (2.99 Å), which were also more numerous than those of prednisolone. MMP2 was designated as the "most promising target" because it exhibited the greatest differential binding between active compounds and control (Compound 19: –9.069 kcal/mol vs. aspirin: –5.883 kcal/mol, a 35% difference), which was larger than the differences observed for IL-6 or MPO. On the MMP2 target (PDB ID: 8H78), Compound 19 showed the lowest binding energy among all tested compounds at -9.069 kcal/mol, which was lower than that of the positive control aspirin (-5.883 kcal/mol) and Compound 12 (-8.608 kcal/mol). Compound 19 formed hydrogen bonds with Ala84 (2.47 Å) and Leu83 (3.07

Å), while aspirin formed hydrogen bonds with Pro141 (2.41 Å) and Tyr143 (3.16 Å). Notably, Compound 12 exhibited a binding energy identical to that of aspirin (-8.608 kcal/mol) but did not form any conventional hydrogen bonds, instead interacting through hydrophobic forces with residues Pro141, Ala140, Leu117, Thr144, Tyr143, Leu138, Val118, and His121. On the MPO target (PDB ID: 6WY0), the native ligand UFA had a binding energy of -10.07 kcal/mol with hydrogen bonds to Arg239 (3.02 Å) and Gln91 (3.08 Å).

Compound 19 showed a binding energy of -7.521 kcal/mol with two hydrogen bonds to Arg333 (3.23 Å) and Glu242 (2.79 Å), while Compound 12exhibited a binding energy of -7.607 kcal/mol with one hydrogen bond to Arg424 (3.13 Å).

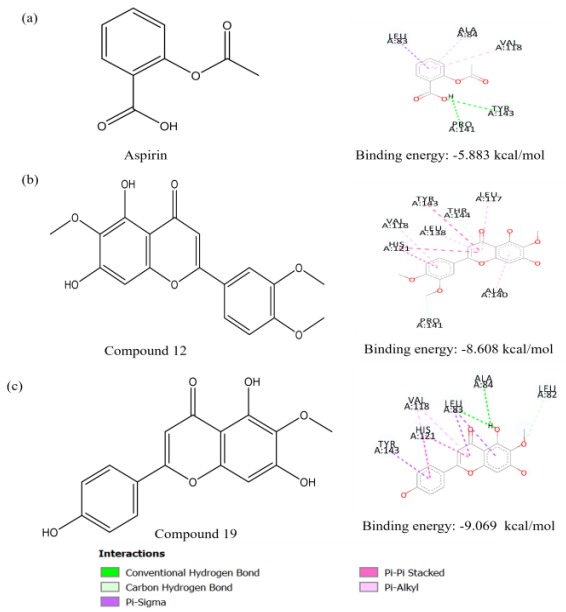

Figure 3: Docking conformations of aspirin, Compound 12, and Compound 19 against MMP2.

Although both test compounds had lower affinity compared to the native ligand UFA, Compound 19 was superior in the number of hydrogen bonds formed for Compound 12. Overall, Compound 19 demonstrated the most superior docking profile as a multi-target candidate for rheuma-toid arthritis therapy, particularly against MMP2 (strongest binding energy) and IL-6 (highest number of hydrogen bonds).

DISCUSSION

This study systematically elucidated the potential molecular mechanisms of the methanolic extract of *L. camara* in the treatment of rheumatoid arthritis (RA) through an integrated approach combining network pharmacology and molecular docking. Our key findings demonstrate that Compound 19 and Compound 12 represent promising multi-target candidates, exhibiting strong binding affinities against IL-6, MMP2, and MPO three central mediators in RA pathogenesis[5,6]. Compound 19 is a naturally occurring flavonoid previously reported to possess anti inflammatory activity through inhibition of NF-κB and MAPK pathways[34]. In RA models, hispidulin suppressed IL-6 and MMP-9 expression in synovial fibroblasts[35]. Our docking results are consistent with these experimental findings, supporting the validity of our *in silico* predictions. To address the limitations of this purely computational study, we propose the following experimental validations: (1) MMP2 inhibition assay using recombinant enzyme; (2) IL-6 suppression assay in RA synovial fibroblast cell line (MH7A); and (3) evaluation of Compound 19 in a collagen-induced arthritis (CIA) mouse model. These experiments are currently being planned for future studies.

The importance of hydrogen bond interactions in ligand-protein binding stability is well established. Previous studies have demonstrated that each hydrogen bond contributes approximately 2–5 kcal/mol to binding affinity and plays a critical role in determining ligand specificity and selectivity[36]. Therefore, the multiple hydrogen bonds formed by Compound 19 with IL-6 (five H-bonds) and MMP2 (two H-bonds) suggest stable and selective inhibition of these key RA-related targets. The identification of 15 overlapping targets between *L. camara* compounds and RA related genes highlights a multi pharmacological mechanism of action, which is a distinct advantage of natural product based therapies over conventional single target agents. Among these targets, IL6, MMP2, and MPO emerged as hub nodes in the PPI network, indicating their crucial roles in bridging multiple pathogenic pathways. IL-6 is a key pro-inflammatory cytokine that drives Th17 cell differentiation, acute phase protein production, and bone erosion in R[4]. MMP2 contributes to extracellular matrix degradation, while MPO is involved in oxidative stress pathways[5]. The ability of *L. camara* compounds to simultaneously target these three proteins suggests a synergistic effect that may address the complexity of RA pathogenesis. This finding aligns with previous network pharmacology studies on herbal medicines for RA[19,28].

Compound 19 exhibited an outstanding docking profile with a binding energy against MMP2 of -9.069 kcal/mol, significantly lower than aspirin (-5.883 kcal/mol), indicating stronger inhibitory potential. Furthermore, the multiple hydrogen bond interactions with key residues in the active site of IL-6 (Ser106, Ser224, Gln158, Ser156, Glu114) suggest stable and specific binding, which may block IL-6 receptor homodimerization and downstream inflammatory signalling. This finding is consistent with the known anti-inflammatory properties of *L. camara* extracts[13,14]. The binding energy of Compound 19 against IL-6 (-6.269 kcal/mol) was comparable to prednisolone (-6.405 kcal /mol), further supporting its therapeutic potential. Compound 12, while showing an identical binding energy to aspirin against MMP2 (-8.608 kcal/mol), relied predominantly on extensive hydrophobic interactions rather than hydrogen bonds. This distinct inhibition mechanism could be advantageous in overcoming drug resistance. However, its lower binding affinity against MPO compared to the native ligand suggests that Compound 19 remains the superior multi target candidate.

The KEGG analysis revealing the highest enrichment in the IL-17 signalling pathway is highly relevant, as IL-17 is a major effector cytokine produced by Th17 cells[5]. IL-6 itself is a potent inducer of Th17 differentiation. By targeting both IL-6 and MMP2, Compound 19 may potentially disrupt the positive feedback loop between inflammation and tissue damage. Moreover, previous studies have demonstrated that IL-17 induces mitochondrial dysfunction and autophagosome formation in fibroblast-like synoviocytes, contributing to apoptosis resistance in RA[6]. The involvement of our identified targets in these pathways suggests that *L. camara* compounds may modulate these pathogenic processes.

Biologic therapies such as IL-6 and IL-17 inhibitors have demonstrated clinical efficacy but are limited by adverse effects, high costs, and accessibility issues[7]. In contrast, Compound 19 as a natural product offers potential advantages including multi-target capability and a potentially better safety profile. The traditional use of *L. camara* in rheumatism, as documented in Indonesian ethnomedicine[13], as well as its reported anti-inflammatory and analgesic properties[12,14], provides an ethnopharmacological basis supporting our findings[23,24].

Limitations of the study

Both network pharmacology and molecular docking are *in silico* approaches requiring experimental validation through *in vitro* and *in vivo* studies. Although 83 compounds were identified, only two were subjected to detailed docking analysis. Target prediction databases have inherent limitations. Moreover, ADMET studies are needed before preclinical trials. The methanolic extract also contains numerous compounds whose interactions remain unknown.

CONCLUSION

This study integrates network pharmacology and molecular docking to reveal that Compound 19 from *L. camara* is a promising multi-target candidate for RA therapy, primarily through inhibition of MMP2 and IL-6. These findings provide scientific justification for the traditional use of *L. camara* in rheumatis and pave the way for developing flavonoid based anti-RA agents. Future work should include *in vitro* enzyme inhibition assays and *in vivo* RA animal models to validate the therapeutic potential of Compound 19 (Hispidulin).

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AUTHOR'S CONTRIBUTIONS

Putri IP: data analysis, molecular docking, writing original draft. **Agustina:** formal analysis, conceptualization. **Reka:** data organization. **Ondjo SR:** critical review, editing. **Ruslin:** supervision. **Arba M:** supervision. Final manuscript was checked and approved by both authors.

DATA AVAILABILITY

The empirical data used to support the study's conclusions are available upon request from the corresponding author.

CONFLICT OF INTEREST

None to declare.

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