ORIGINAL ARTICLE

Integrative multi-omics, network pharmacology, and molecular simulation of herbal compounds targeting immune tolerance mechanisms in food allergy

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ABSTRACT

Food allergies (FAs) significantly impact quality of life. Allergen-specific immunotherapy (AIT) shows promise but faces limitations such as prolonged treatment duration, systemic side effects, and poor compliance, especially in pediatric and elderly populations. Complementary and alternative medicine (CAM) may enhance AIT efficacy and safety, yet the mechanisms underlying immune tolerance remain poorly understood. This study employed an integrated *in silico* approach combining network pharmacology, molecular simulation, and metabolomics to investigate anti-allergic *Jamu* medicinal plants in FA. Active compounds from 13 medicinal plants were analyzed to predict key targets and pathways. Molecular docking and dynamics simulations assessed compound-target binding affinities, while metabolomics evaluated tissue distribution and bioavailability in lymphoid tissues. The results identified transforming growth factor-beta 1 (TGFB1) as a key target associated with the FoxO signaling pathway and Th17 cell differentiation, both of which are critical for promoting allergic tolerance. MAPK1 and MAPK14 emerged as additional targets, providing insights into the mechanisms of allergy development. Molecular simulations demonstrated strong binding affinities, with quercetin (−9.1 kcal/mol) and genistein (−8.1 kcal/mol) binding to TGFB1, and isoprocurcumenol (−7.1 kcal/mol) and dicinnamoylmethane (−10.1 kcal/mol) binding to MAPK1 and MAPK14, respectively. Metabolomic analysis further showed high genistein accumulation in lymph nodes. In summary, these findings suggest that CAM-AIT integration could significantly improve FA therapeutic outcomes by promoting immune tolerance and modulating inflammatory pathways.

Key words: Allergen immunotherapy, allergy tolerance, complementary medicine, quality of life, well-being

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INTRODUCTION

Food allergies (FAs) are a major global health problem caused by inappropriate immune responses to food allergens, affecting individuals of all ages and more than 500 million people worldwide.[1] Although current allergy therapies effectively control symptoms, they are not curative, prompting interest in disease-modifying approaches such as allergen-specific immunotherapy (AIT) and complementary and alternative medicine (CAM).[2,3]

Bioactive compounds from medicinal plants play an important role in drug discovery through immune modulation.[4,5] CAM is widely used, with up to 50% of allergy patients reporting use, largely due to perceived safety.[3,6] However, clinical evidence for herbal therapies in FA remains limited; for example, FAHF-2 was well tolerated but showed modest efficacy.[7] Emerging evidence suggests that allergen-specific tolerance is enhanced when CAM is combined with allergen exposure or immunotherapy, supporting CAM–AIT integration as a promising strategy for FA treatment.[2,7-9] Medicinal plants have been widely studied as complementary therapies for allergy treatment,[3,4,6-9] yet their immunomodulatory mechanisms remain poorly understood. This study aimed to identify key targets and signaling pathways involved in allergic tolerance induced by natural compounds from antiallergic medicinal plants, providing support for the development of complementary strategies to enhance FA tolerance.

MATERIALS AND METHODS

Screening natural products of medicinal plant

Thirteen medicinal plants with empirically demonstrated antiallergic activity were included in this study [Supplementary Information 1]; detailed protocols are provided in the Supplementary Methods.

Prediction of natural product targets and allergy tolerance-related genes

Target prediction and gene collection were performed using multiple curated databases. Full details of the databases used and data processing procedures are described in the Supplementary Methods.

Data integration, Venn analysis, and construction of the protein–protein interaction network

Protein–protein interaction (PPI) network was constructed using the STRINGdb package in RStudio v4.3.2; details are provided in the Supplementary Methods

Gene ontology enrichment and Kyoto Encyclopedia of Genes and Genomes signal pathway analysis

Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were implemented using the clusterProfiler package in RStudio v4.3.2; details are provided in the Supplementary Methods.

Molecular docking, spatial metabolomic analysis, and molecular dynamics simulation

Molecular docking, metabolomic analysis, and molecular dynamics (MD) simulations were conducted using AutoDock Vina, MetaboAnalyst 6.0, and AMBER20, respectively, following standard protocols [Supplementary Methods].

RESULTS

Integrating multi-omics dataset for allergy tolerance

Out of 257 selected natural compounds, 157 were analyzed for target prediction, yielding 1317 unique target genes after duplicate removal. A total of 3254 unique allergy tolerance-related genes were compiled from six databases [Supplementary Information 1]. Intersection analysis identified 569 overlapping genes, as shown in the Venn diagram [Figure 1a].

Protein–protein interaction network analysis

A PPI network was constructed, revealing dense connectivity [Figure 1b]. The top 20 hub genes were identified using four centrality algorithms [Figure 1c-f], with node color intensity indicating interaction strength. Key hub genes, including STAT3, Interleukin-6 (IL-6), tumor necrosis factor (TNF), transforming growth factor-beta 1 (TGFB1), IFNG, AKT1, JUN, IL-1B, and PTGS2, were consistently highly ranked and associated with allergic regulation.

Gene ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis

GO enrichment analysis identified 3,163 biological process (BP), 298 molecular function (MF), and 115 cellular component (CC) terms. Enriched BPs were mainly related to cytokine regulation, inflammatory responses, leukocyte migration, and MAPK signaling, while key MFs involved kinase activity and cytokine receptor binding. CC analysis highlighted the raft domain, apical membrane, and secretory granule lumen [Figure 2a and Supplementary Information 2].

A total of 199 KEGG pathways were identified, with the top seven most relevant to FA tolerance shown in Figure 2b [Supplementary Information 2]. Key targets were enriched in the PI3K/AKT, apoptosis, FoxO signaling, Th17 cell differentiation, TNF signaling, PD-1/PD-L1 checkpoint, and cAMP signaling pathways, all of which are involved in immune regulation and allergic tolerance.

Natural compounds-target genes-critical pathway network

Our findings identified TGFB1 as the top gene across all GO categories and were linked to the FoxO signaling pathway

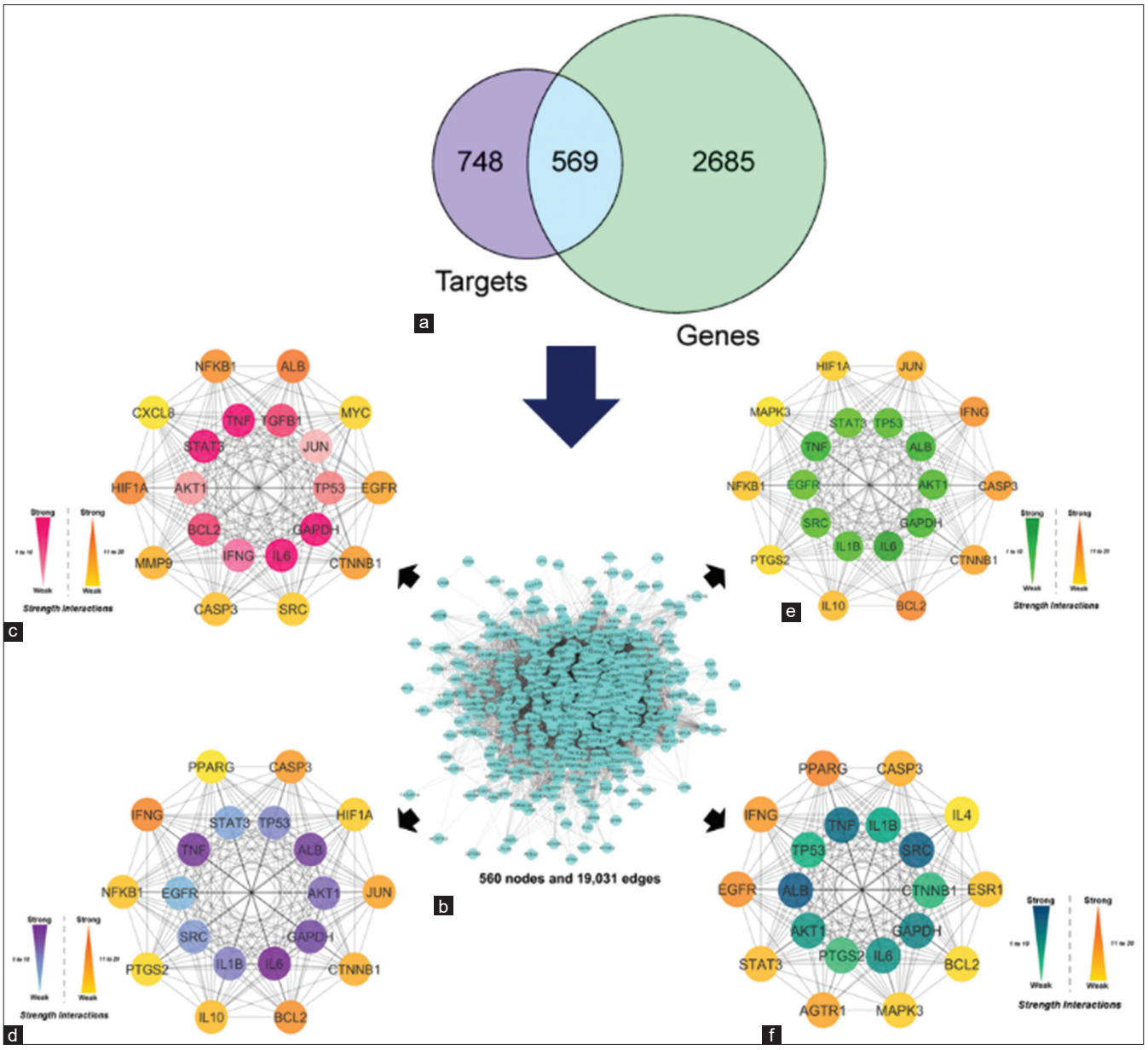

Figure 1: Identification and network constructions of potential food allergie (FA) tolerance-related targets. (a) Overlapping genes between natural compounds (blue) and FA tolerance (green), (b) protein–protein interaction network construction, (c-f) Top 20 hub genes ranked by maximal clique, degree, closeness, and betweenness centrality

and Th17 cell differentiation. MAPK1 and MAPK14 were also prominent in BP and CC categories. KEGG analysis showed that MAPK1 was involved in all top seven pathways, while MAPK14 participated in PD-1/PD-L1, TNF, Th17 differentiation, and FoxO signaling pathways. Consistent with the PPI analysis, these findings highlight the role of the MAPK cascade in allergy development.[10] Consequently, TGFB1, MAPK1, and MAPK14 were selected as targets for molecular docking [Figure 3a].

Molecular docking

Molecular docking was performed to support the network pharmacology analysis by comparatively evaluating the binding affinities (ΔG) of selected natural compounds to TGFB1, MAPK1, and MAPK14 relative to their native ligands [Supplementary Information 3]. The top-ranked binding energies compared with native ligands are summarized in Table 1. The docked compounds exhibited interaction patterns comparable to native ligands, suggesting shared mechanisms of action and comparable pharmacological activity [Figure 4 and Supplementary Information 3].

Quercetin and genistein showed high similarity in interacting residues with TGFB1 (92% and 62%, respectively), with moderate similarity in interaction

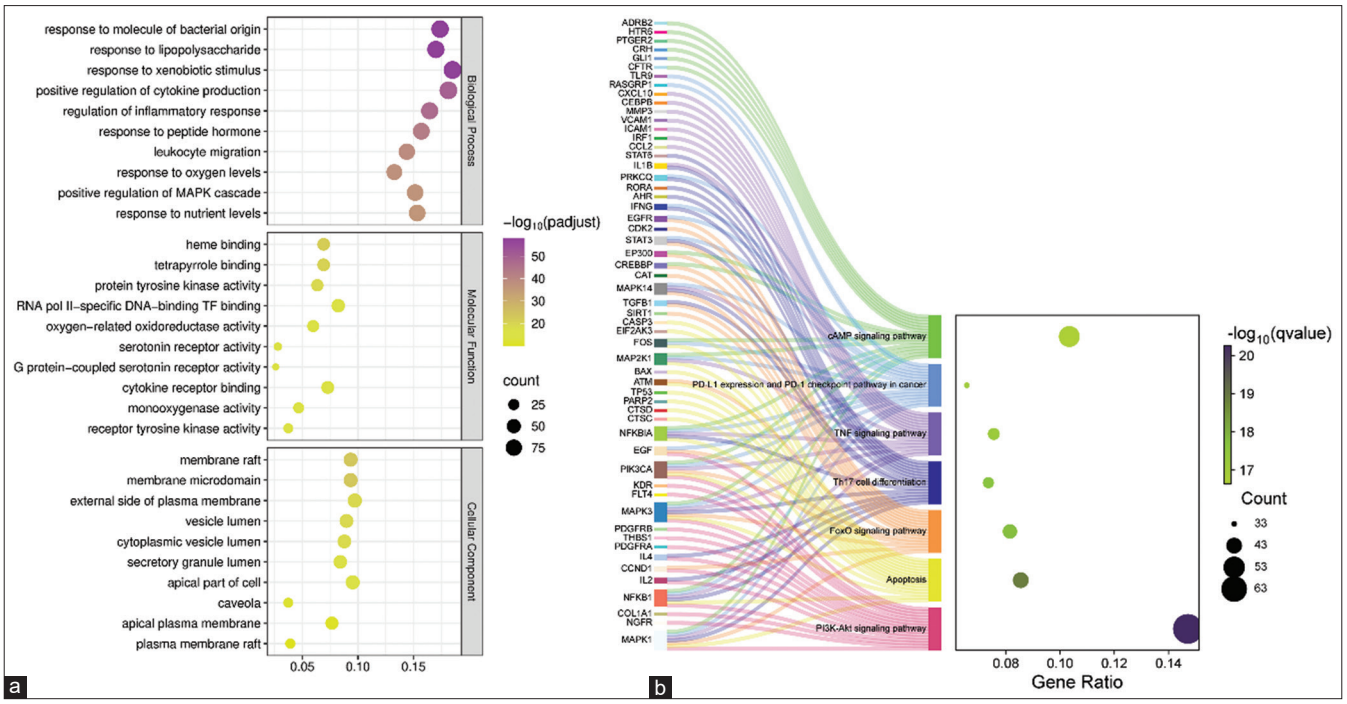

Figure 2: Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment of food allergy tolerance induction. (a) Top 10 enriched GO terms in biological process, molecular function, and cellular component categories, (b) Top seven KEGG pathways and associated hub genes

Table 1: Top-ranked docking scores of natural compounds against selected targets

Receptor	Natural compound	ΔG (kcal/mol)
TGFB1 (4X0M)	Quercetin	−9.1
	Genistein	−8.1
	3WA (Native Ligand)	−5.5
MAPK1 (4ZXT)	Isoprocurcumenol	−7.1
	Corymbolone	−6.1
	Turmeronol B	−6.1
	(5S,6R)-5-Hydroxy-2-methyl-6-(4-methylphenyl)-2-hepten-4-one	−6.0
	(+)-ar-Turmerone	−5.8
	1,10-Dehydro-10-deoxy-9-oxozedoarondiol	−5.8
	6α-Hydroxycurcumanolide A	−5.6
	Caffeic acid	−5.5
	Procurcumenol	−5.5
	Epiprocurcumenol	−5.4
	Turmeronol A	−5.4
	4,8-Dimethyl-3,7-nonadien-2-ol	−5.0
	2-Ethyldodecanoic acid	−4.8
	Lauric acid	−4.8
	Octadecanoic acid	−4.8
	α-Linolenic acid	−4.5
	CAQ (Native Ligand)	−4.4
MAPK14 (4DLI)	Dicinnamoylmethane	−10.1
	Tembetarine	−10.1
	RL87 (Native Ligand)	−9.8

3WA: 4-aminopyrido[2,3-d] pyrimidin-5 (8H)-one, CAQ: Catechol, RL87: N~4~-cyclopropyl-2-phenylquinazoline-4,7-diamine

types (38% and 31%) compared to the native ligand. For MAPK1, isoprocurcumenol and corymbolone exhibited complete (100%) residue similarity and 40% similarity in interaction types, while dicinnamoylmethane and tembetarine showed 90% residue similarity and 30% interaction type similarity. For MAPK14, dicinnamoylmethane and tembetarine demonstrated 82% and 94% residue similarity, with interaction type similarities of 41% and 47%, respectively. Notably, dicinnamoylmethane showed stronger binding than tembetarine, possibly due to greater van der Waals interactions.[11,12]

Analysis of spatial metabolomics for the top hit compound

Metabolomic analysis was performed on the top two docked compounds to assess their biological and tissue-specific localization related to allergic tolerance. Our results showed that genistein, quercetin, kaempferol, tembetarine, isoprocurcumenol, and turmeronol B were identified as eligible candidates [Supplementary Information 3], while compounds not listed in the human metabolome database were excluded due to limited metabolomic information. Interestingly, we found that genistein was detected in 14 of 16 tissues, with the highest enrichment in lymph nodes [Figure 3b]. Given the central role of lymph nodes in T cell-mediated immunity, these results suggest that genistein may support allergic tolerance through modulation of adaptive immune responses.

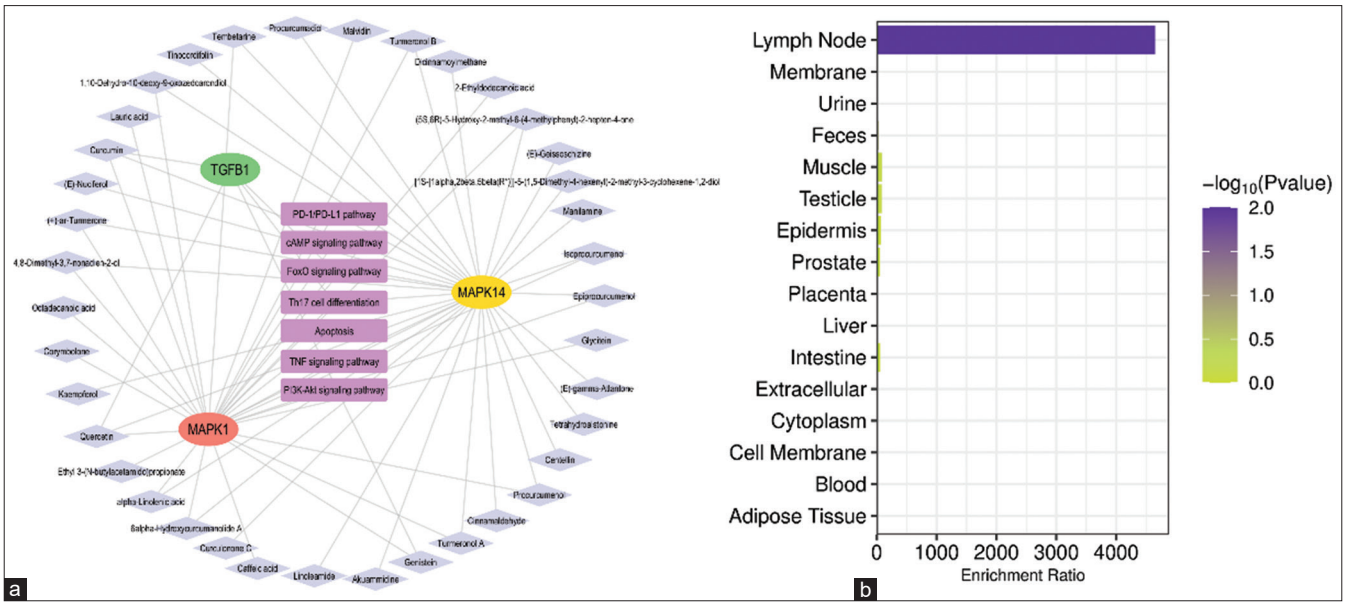

Figure 3: Network construction and metabolite set enrichment analysis. (a) Visualization of natural compounds, target genes, and signaling pathways. The oval shape represents critical target genes, while the violet rectangle shape represents potential signaling pathways. The top-hit natural compounds are shown in a light-blue diamond structure, (b) Tissue-specific and biological localization profiles of selected compounds based on enrichment ratio (ER). ER >1 indicates overrepresentation, ER = 1 indicates no enrichment, and ER <1 indicates underrepresentation of the compound in the biological process analyzed

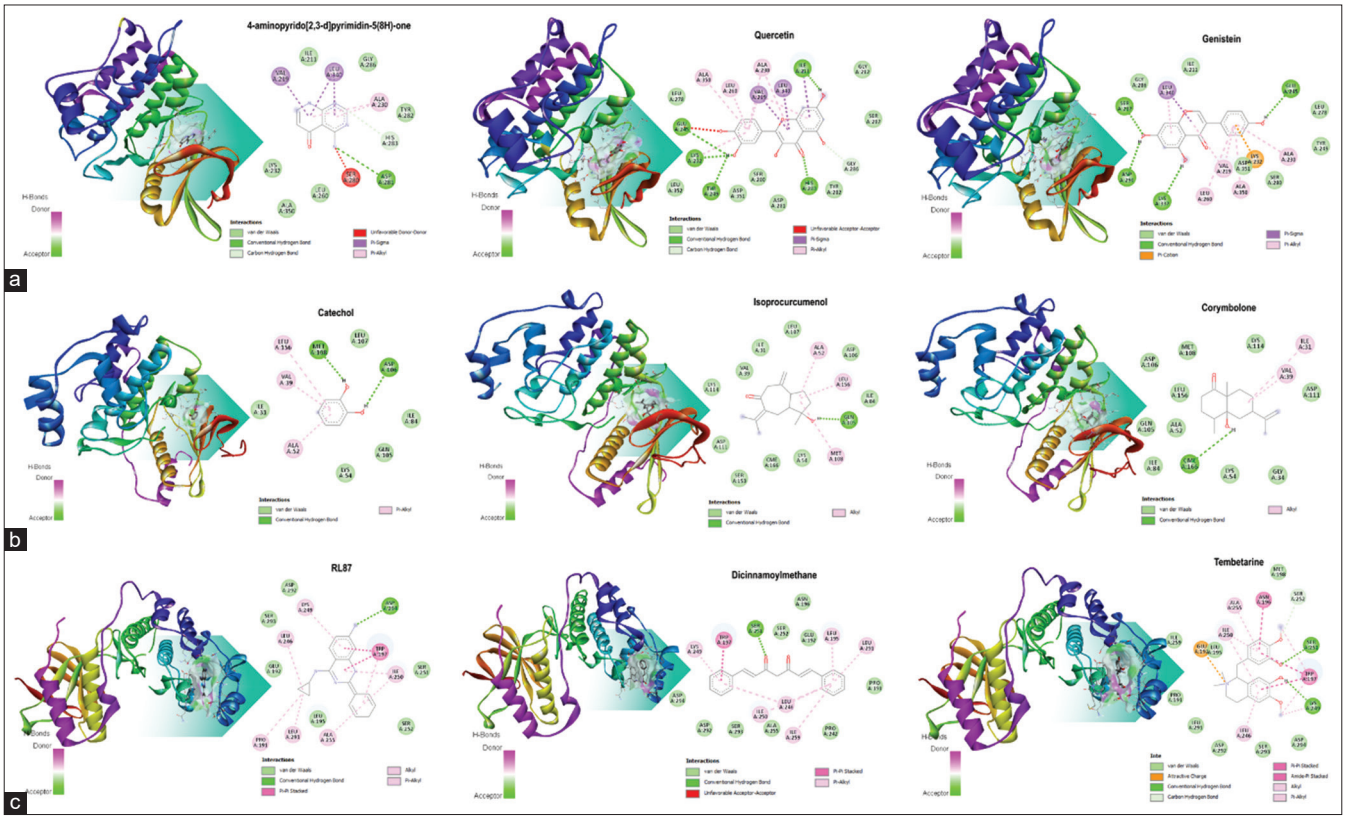

Figure 4: Intermolecular interactions of selected natural compounds with (a) TGFβ-1 (top), (b) MAPK1 (middle), and (c) MAPK14 (bottom)

Molecular dynamics simulation

As shown in Figure 5a, the quercetin-TGFB1 complex reached a stable RMSD (~1.5–1.6Å) from 30 to 90 ns, followed by a slight increase to 1.8Å toward the end of the simulation. In contrast, while the genistein–TGFB1 complex stabilized later (70–100 ns) at ~1.3–1.4Å,

indicating greater stability for quercetin, with RMSD values ranging from 1.3 to 1.4Å, suggesting quercetin forms a more stable complex with TGFB1 compared to genistein. The isoprocurcumenol–MAPK1 complex stabilized during the final 10 ns at ~1.7Å [Figure 5b], and the dicinnamoylmethane–MAPK14 complex remained stable from 30 to 70 ns with RMSD values of ~2.0–2.1Å before increasing fluctuations [Figure 5c].

Our RMSF results revealed that the quercetin-TGFB1 complex exhibited low fluctuation at residues Ile202, Met205, Phe209, Tyr203, and Leu207. Similarly, in the genistein-TGFB1 complex, residues with low RMSF included Ile202, Tyr203, Met205, Asp201, and Phe209, suggesting binding to the same active site on TGFB1 [Figure 6a]. Furthermore, stable residue patterns were observed for the isoprocurcumenol–MAPK1 complex, with low fluctuations at Trp204, Ile203, Met284, Gly207, and Val206 [Figure 6b]. Likewise, the dicinnamoylmethane–MAPK14 complex showed low RMSF values at Ile186, Met268, Gly190, Val189, and Leu264 [Figure 6c].

MM-GBSA analysis showed that quercetin–TGFB1 and genistein–TGFB1 complexes were mainly stabilized by van der Waals interactions, indicating hydrophobic binding sites. In contrast, isoprocurcumenol–MAPK1 and dicinnamoylmethane–MAPK14 complexes were dominated by electrostatic interactions, suggesting more hydrophilic active sites. Among the top hit compounds [Supplementary Information 3], quercetin–TGFB1 showed the most favorable binding free energy (ΔG = −24.3813 kcal/mol), followed by the genistein-TGFB1 complex (ΔG = −22.6993 kcal/mol), indicating that quercetin has a stronger binding affinity toward TGFB1. The isoprocurcumenol-MAPK1 and dicinnamoylmethane-MAPK14 complexes exhibited ΔG values of −12.0327 kcal/mol and −19.2243 kcal/mol, respectively, supporting quercetin as a promising candidate for further investigation.

DISCUSSION

FAs are a major global health concern, particularly in children and adolescents, and can cause life-threatening reactions and long-term psychological effects.[13] Although AIT is promising, safety and compliance remain major challenges.[14,15] Growing evidence suggests that CAM may support allergy prevention and treatment,[3,8] and its integration with AIT could enhance efficacy while reducing side effects.[2,8] However, the molecular mechanisms underlying FA tolerance induced by natural compounds remain unclear. To address this, we performed an *in silico* analysis of 13 Jamu medicinal plants with reported antiallergic potential.[4,16]

Basically, T lymphocytes are central to immune tolerance, and disruption of T-cell regulation promotes Th2 responses, immunoglobulin E production, and allergic inflammation.[17] Our PPI analysis identified STAT3, IL-6, TNF, TGFB1, IFNG,

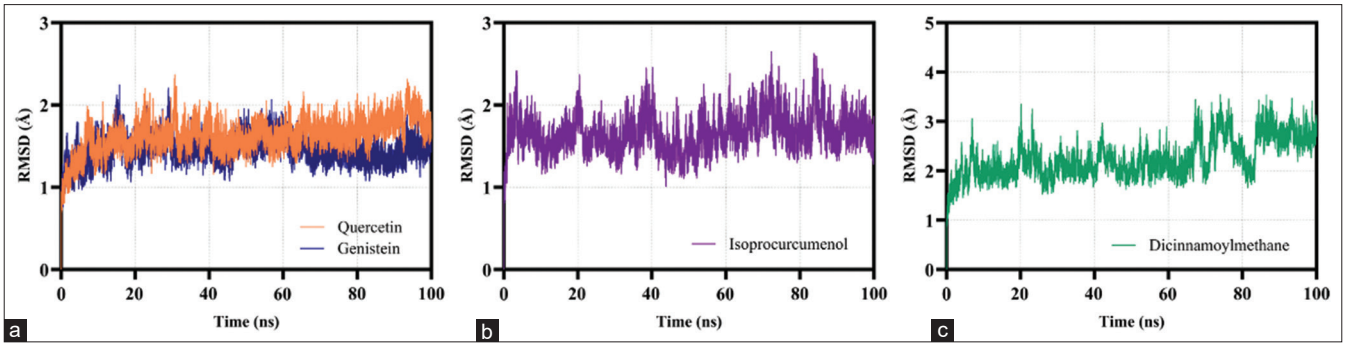

Figure 5: RMSD plots of protein–ligand complexes: (a) Quercetin and Genistein with transforming growth factor-beta 1, (b) Isoprocurcumenol with MAPK1, and (c) Dicinnamoylmethane with MAPK14

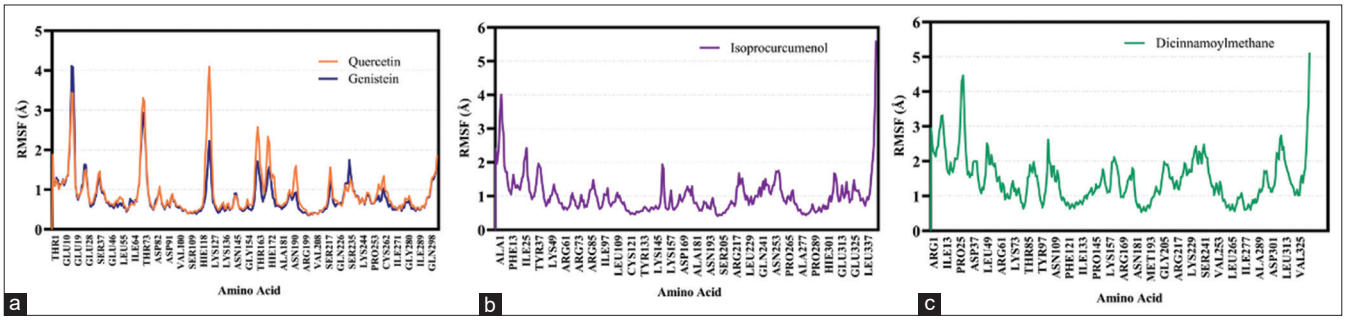

Figure 6: RMSF plots of protein–ligand complexes: (a) Quercetin and Genistein with transforming growth factor-beta 1, (b) Isoprocurcumenol with MAPK1, and (c) Dicinnamoylmethane with MAPK14

AKT1, JUN, IL-1 β, and PTGS2 as key tolerance-related genes.[18,19] Functional and pathway analyses highlighted TGFB1, MAPK1, and MAPK14 as central regulators, implicating FoxO signaling, Th17 differentiation, and the MAPK cascade in allergy suppression. TGF-β-mediated signaling governs the balance between Treg and Th17 cells through SMAD-dependent and MAPK/PI3K-AKT pathways, and its dysregulation contributes to allergic disease.[18-22]

Treg and Th17 cells are key regulators of allergic tolerance, with enhanced Treg survival observed in peanut-allergic patients undergoing long-term oral immunotherapy.[23] FoxO signaling, particularly FoxO1 and FoxO3, is essential for Treg function by regulating FoxP3 expression and suppressing Th17 differentiation.[24-26] Loss of FoxO1 and FoxO3 in T cells leads to severe systemic inflammation due to Treg dysfunction, underscoring its role in immune tolerance.[24,27] Given this mechanistic framework, molecular docking and MD simulations identified quercetin and genistein as leading candidates targeting TGFB1, isoprocurcumenol and corymbolone for MAPK1, and dicinnamoylmethane and tembetarine for MAPK14, with interaction patterns comparable to native ligands.[28] MD analyses supported docking results, identifying quercetin as the most stable candidate. Notably, metabolomic enrichment revealed that genistein accumulates in lymph nodes, key sites of immune regulation, supporting its potential relevance in immunotherapy.[29]

CONCLUSION

This integrated study highlights the potential of Jamu medicinal plants in FA management. TGFB1, MAPK1, and MAPK14 were identified as key immune tolerance-related targets, with quercetin and genistein emerging as candidate compounds potentially involved in regulating the Treg/Th17 balance. The preferential lymph-node localization of genistein suggests possible systemic immunomodulatory relevance. These findings support selected herbal compounds as promising adjuncts to AIT, although further preclinical and clinical validation is required.

Acknowledgment

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Conflicts of interest

There are no conflicts of interest.

Supplementary information

The supplementary information supporting this study is publicly available and can be accessed and downloaded at: https://doi.org/10.5281/zenodo.19028988.

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