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Integrated Network Pharmacology, Molecular Docking, and Computational Meta-Analysis of Phytoconstituents Targeting Gut–Brain Axis Associated Inflammatory Pathways

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Abstract: *Objectives: Gut–brain axis (GBA) dysregulation contributes significantly to chronic inflammatory disorders through interconnected neuroimmune, endocrine, and microbial mechanisms. The present study aimed to evaluate selected phytoconstituents for their therapeutic potential against GBA-associated inflammatory pathways using an integrated network pharmacology, molecular docking, and computational meta-analysis approach.*

Materials and Methods: Eight phytoconstituents, namely Apigenin, Fisetin, Berberine, Epigallocatechin Gallate (EGCG), Rosmarinic Acid, Withaferine A, Palmatine, and Hesperidin, were subjected to drug-likeness and ADME evaluation using MolSoft and SwissADME. Potential targets were identified using SwissTargetPrediction and intersected with GBA-associated inflammatory targets. Priority targets were selected through VarElect analysis and further investigated through STRING-based protein–protein interaction analysis, Cytoscape network construction, KEGG pathway enrichment, and molecular docking using AutoDock Vina. Computational meta-analysis was performed using ANOVA, Pearson correlation, hierarchical clustering, and composite meta-scoring.

Results:

Six phytoconstituents exhibited complete Lipinski compliance. Berberine demonstrated the highest drug-likeness score (0.77), followed by Palmatine (0.69) and Hesperidin (0.59). Target prediction identified key inflammatory mediators including ALOX5, ALOX5AP, MAPKs, JAK2, STAT3, TNF, IL2, MAOA, and MMP2. Molecular docking revealed strong binding interactions, with EGCG exhibiting the highest affinity towards ALOX5AP (−10.0 kcal/mol) and Withaferine A displaying the broadest multi-target activity profile. Computational meta-analysis ranked Withaferine A as the lead candidate based on target coverage, docking performance, and composite MetaScore.

Conclusions: The integrated computational analysis identified Withaferine A and EGCG as promising multi-target phytoconstituents against GBA-associated inflammatory pathways. These findings provide a scientific basis for future experimental validation and development of phytoconstituent-based therapeutic strategies for inflammatory disorders.

Keywords: Gut–Brain Axis; Network Pharmacology; Molecular Docking; Phytoconstituents; Inflammation; Computational Meta-analysis

I. INTRODUCTION

The gut–brain axis (GBA) is a complex bidirectional communication network integrating the gastrointestinal tract, gut microbiota, enteric nervous system, immune system, and central nervous system.(1) Through neural, endocrine, immune, and metabolic pathways, the GBA plays a crucial role in maintaining physiological homeostasis. Dysregulation of this

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axis contributes to the development of inflammatory bowel disease, neuroinflammation, depression, anxiety, metabolic disorders, and neurodegenerative diseases.(2)

Recent evidence highlights the importance of microbial metabolites, short-chain fatty acids, neurotransmitters, and immune mediators in regulating GBA signalling. Alterations in microbial composition and function can increase intestinal permeability, promote systemic inflammation, activate toll-like receptor signalling, and stimulate pro-inflammatory cytokine production.(3) These mechanisms contribute to chronic inflammatory conditions affecting both the gastrointestinal tract and the central nervous system.(4) Consequently, the modulation of common inflammatory signaling pathways, such as those involving TNF and IL-17, has emerged as a viable therapeutic strategy for restoring GBA homeostasis and mitigating neurodegenerative progression.(5)

Conventional anti-inflammatory therapies frequently target single pathways and may be associated with adverse effects, incomplete responses, and therapeutic resistance. Consequently, there is growing interest in phytoconstituents possessing multi-target pharmacological activities.(6) Natural compounds such as flavonoids, alkaloids, polyphenols, and steroidal lactones exhibit anti-inflammatory, antioxidant, neuroprotective, and microbiota-modulating properties that may be beneficial in GBA-associated disorders.(7)

Network pharmacology has emerged as a powerful systems biology approach capable of identifying complex interactions among compounds, targets, and biological pathways. Combined with molecular docking and computational meta-analysis, this approach enables the identification of promising multi-target therapeutic candidates.(8)

Therefore, the present study was designed to investigate selected phytoconstituents through integrated drug-likeness assessment, target prediction, network pharmacology analysis, molecular docking, and computational meta-analysis to identify potential therapeutic candidates against GBA-associated inflammatory pathways.(9) By elucidating the mechanistic interactions between these secondary metabolites and key signaling proteins, this research aims to bridge the gap between traditional herbal medicine and molecular insights into gut-mediated neuroinflammation .(10)

Materials and Methods

Selection of Phytoconstituents

Eight phytoconstituents with documented anti-inflammatory, antioxidant, and neuroprotective activities were selected through an extensive literature survey: Apigenin, Fisetin, Berberine, Epigallocatechin Gallate (EGCG), Rosmarinic Acid, Withaferine A, Palmatine, and Hesperidin. These compounds were chosen based on their reported efficacy in modulating gut microbiota composition, regulating inflammatory mediators, and influencing gut–brain axis signaling pathways.

Drug-Likeness and ADME Analysis

Drug-likeness and pharmacokinetic properties of the selected phytoconstituents were evaluated using MolSoft Molecular Property Prediction and SwissADME platforms.(11) Parameters assessed included molecular weight, hydrogen bond donor (HBD) count, hydrogen bond acceptor (HBA) count, topological polar surface area (TPSA), lipophilicity (LogP), aqueous solubility, blood–brain barrier (BBB) permeability, and compliance with Lipinski's Rule of Five. MolSoft drug-likeness scores were also recorded to assess the overall drug-like potential of each compound.(12)

Target Prediction and Prioritization

Potential molecular targets of the selected phytoconstituents were identified using the SwissTargetPrediction database based on chemical similarity and known ligand–target interactions. Disease-associated targets related to gut–brain axis inflammation were retrieved from the GeneCards database.(13) The predicted phytoconstituent targets were compared with disease-associated targets to identify common targets through Venn analysis. Subsequently, the common targets were prioritized using the VarElect platform according to disease relevance scores and functional associations with inflammatory pathways.

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Network Pharmacology Analysis

Protein–protein interaction (PPI) networks of the prioritized targets were constructed using the STRING database and visualized using Cytoscape software. Network topology analysis was performed to identify hub targets based on connectivity and interaction patterns. Functional enrichment and KEGG pathway analyses were conducted to determine the major biological processes and signaling pathways associated with the prioritized targets, with particular emphasis on inflammatory and neuroimmune pathways.(14)

Molecular Docking

Molecular docking studies were performed using AutoDock Vina integrated within the PyRx virtual screening platform. Three-dimensional structures of target proteins were obtained from the Protein Data Bank (PDB), while ligand structures were retrieved from the PubChem database. Prior to docking, protein and ligand structures were prepared by removing water molecules, adding hydrogen atoms, and optimizing molecular geometries. Binding affinities were calculated and expressed as binding free energies (kcal/mol), with lower docking scores indicating stronger predicted binding interactions.(15)

Computational Meta-Analysis

Computational meta-analysis was conducted to comparatively evaluate the pharmacological performance of the selected phytoconstituents. Statistical analyses were performed using Microsoft Excel and GraphPad Prism. One-way ANOVA was employed to assess differences in docking affinity distributions among compounds, while Pearson correlation analysis was used to examine the relationship between drug-likeness scores and docking affinities.(16)Hierarchical clustering and heatmap analyses were performed to identify patterns of target interactions and compound similarity. Additionally, a composite MetaScore integrating docking affinity, target coverage, and drug-likeness parameters was calculated to rank the phytoconstituents according to their overall therapeutic potential.(15)

Results

Drug-Likeness and ADME Profiling

Drug-likeness and ADME assessment revealed acceptable pharmacokinetic characteristics for most of the selected phytoconstituents. Berberine demonstrated the highest MolSoft drug-likeness score (0.77), followed by Palmatine (0.69) and Hesperidin (0.59). EGCG exhibited the lowest score (0.23) due to multiple Lipinski's Rule of Five violations. Most compounds showed favorable physicochemical properties and moderate blood–brain barrier permeability, supporting their potential application in gut–brain axis-associated inflammatory disorders. Detailed ADME parameters and drug-likeness scores are summarized in Table 1, while representative SwissADME and MolSoft analyses are presented in Figure 1.

Target Prediction and Prioritization

Potential molecular targets of the selected phytoconstituents were identified using SwissTargetPrediction. A total of 51 cumulative targets were predicted, representing diverse protein classes associated with inflammatory and neuroimmune pathways. Disease-associated targets related to gut–brain axis inflammation were retrieved from the GeneCards database. The common targets were subsequently prioritized using VarElect based on disease relevance scores, resulting in the identification of fifteen high-confidence targets for downstream analyses. SwissTargetPrediction results, GeneCards-derived targets, and VarElect prioritization outputs are presented in Figures 2–4, respectively.

Network Pharmacology Analysis

Protein–protein interaction analysis revealed extensive interactions among the prioritized targets and identified several hub proteins involved in inflammatory signaling pathways. Network topology analysis highlighted TNF, JAK2, STAT3, MAPK family proteins, ALOX5, and ALOX5AP as central regulatory nodes. STRING-derived protein–protein

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interaction networks and Cytoscape-based compound–target interaction networks are illustrated in Figures 5 and 6, respectively. KEGG pathway enrichment analysis identified the MAPK signaling pathway as a major pathway associated with the prioritized targets (Figure 7).

Molecular Docking Analysis

Molecular docking studies demonstrated strong interactions between the selected phytoconstituents and prioritized inflammatory targets. EGCG exhibited the strongest binding affinity toward ALOX5AP (−10.0 kcal/mol), whereas Withaferine A displayed broad-spectrum activity across multiple targets. Fisetin and Hesperidin showed notable affinity toward MMP2, indicating potential roles in extracellular matrix regulation and inflammatory modulation. Representative protein–ligand interactions are shown in Figure 8, while the corresponding docking affinities are summarized in Table 2 and Table 3.

Computational Meta-Analysis

Computational meta-analysis was performed to comparatively evaluate the pharmacological performance of the selected phytoconstituents. One-way ANOVA demonstrated no statistically significant difference among overall docking affinity distributions ($p > 0.05$). Pearson correlation analysis revealed a weak positive association between drug-likeness scores and docking affinities ($r = 0.16$, $p = 0.425$). Hierarchical clustering identified distinct phytoconstituent groups based on target interaction patterns, while MetaScore ranking highlighted Withaferine A as the lead candidate owing to its superior target coverage and overall docking performance. The integrated computational meta-analysis results are presented in Figures 9.

Discussion

The present study identified ALOX5AP, MAOA, MMP2, MAPK family proteins, and TNF-related signaling as important targets involved in gut–brain axis-associated inflammatory pathways. ALOX5AP is closely associated with leukotriene biosynthesis and inflammatory mediator production.(17) Strong binding of EGCG and Withaferine A toward ALOX5/ALOX5AP suggests their possible role in suppressing leukotriene-mediated inflammatory responses.

MAOA is involved in monoamine metabolism and has relevance in neuroimmune regulation. The strong interaction of Withaferine A and Fisetin with MAOA indicates potential involvement in neuroinflammatory modulation and gut–brain axis signaling.(18) Similarly, MMP2 plays an important role in extracellular matrix remodeling, intestinal barrier integrity, and inflammatory tissue damage. The higher affinity of Hesperidin and Fisetin toward MMP2 suggests their possible protective role in maintaining gut barrier function.(19)

MAPK signaling is a central inflammatory pathway involved in cytokine production, oxidative stress, immune activation, and neuronal inflammation. The docking interaction of selected phytoconstituents with MAPK targets supports their possible multi-target anti-inflammatory potential. TNF signaling is another major pathway involved in systemic inflammation, IBD, and neuroinflammatory disorders.(20) Although direct docking affinity toward TNF was comparatively lower, phytoconstituents may still regulate TNF-mediated inflammation indirectly through upstream pathways such as MAPK, NF-κB, and JAK-STAT signaling.(21)

Overall, Withaferine A and EGCG showed strong multi-target interaction profiles, supporting their potential as lead phytoconstituents for gut–brain axis-associated inflammatory disorders. However, these findings are based on computational prediction and molecular docking; therefore, experimental validation through in vitro and in vivo studies is necessary.(22)

II. CONCLUSION

The present study employed an integrated network pharmacology, molecular docking, and computational meta-analysis approach to evaluate the therapeutic potential of selected phytoconstituents against gut–brain axis-associated inflammatory pathways. Drug-likeness and ADME analyses demonstrated favorable pharmacokinetic characteristics for

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most compounds, while target prediction and network pharmacology analyses identified key inflammatory mediators, including ALOX5AP, MAOA, MMP2, MAPK family proteins, and TNF-associated signaling pathways. Molecular docking revealed strong target interactions, with EGCG exhibiting the highest binding affinity and Withaferine A demonstrating the broadest multi-target activity profile. Computational meta-analysis further identified Withaferine A as the lead candidate based on target coverage, docking performance, and overall MetaScore ranking. These findings suggest that selected phytoconstituents possess promising multi-target therapeutic potential against gut–brain axis-associated inflammatory disorders and warrant further experimental validation through in vitro and in vivo studies.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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The authors declare that no external funding was received for this study.

Ethical Approval

This study was entirely computational and did not involve human participants, animals, or patient-derived samples. Therefore, ethical approval was not required.

Data Availability Statement

All data generated or analysed during this study are included in this published article and its supplementary materials. Additional data may be made available by the corresponding author upon reasonable request.

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Table

Table 1. Drug-Likeness Scores and ADME Parameters (MolSoft / SwissADME)

Compound	Formula	MW (Da)	HBA	HBD	LogP	TPSA (Å²)	BBB Score	Dl Score	Ro5 Viol.
Apigenin	$C_{15}H_{10}O_5$	270.05	5	3	3.22	73.57	2.97	0.39	0
Fisetin	$C_{15}H_{10}O_6$	286.05	6	4	1.35	86.06	2.79	0.46	0
Berberine	$C_{20}H_{18}NO_4$	336.12	4	0	4.39	33.45	4.64	0.77	0
EGCG	$C_{22}H_{18}O_{11}$	458.08	11*	8*	1.44	158.72	1.31	0.23	2
Rosmarinic Acid	$C_{18}H_{16}O_8$	360.08	8	5	1.54	114.28	2.30	0.37	0
Withaferin A	$C_{28}H_{38}O_6$	470.62	5	2	3.83	95.08	2.50	0.37	0
Palmatine	$C_{21}H_{22}NO_4$	352.15	4	0	3.96	31.60	4.64	0.69	0
Hesperidin	$C_{16}H_{14}O_6$	302.08	6	3	2.51	78.55	2.89	0.59	0

Table 2. Auto-Dock Vina Binding Affinities ΔG (kcal/mol) – Targets 1-8

Compound	ALOX5	ALOX5AP	IL2	ITGB1	ITGB2	JAK2	MAOA	MAPK(p38)
Apigenin	-8.4	-6.0	-6.6	-6.9	-6.4	-6.4	-7.9	-7.1
Berberine	-6.7	-9.6	-7.1	-7.2	-6.7	-6.9	-7.5	-6.6
Fisetin	-6.7	-6.5	-6.6	-7.2	-6.3	-6.0	-8.9	-7.2
EGCG	-8.9	-10.0	-7.5	-7.8	-7.7	-6.4	-8.2	-6.8
Palmatine	-7.4	-6.1	-6.3	-6.7	-6.4	-6.3	-7.6	-6.1
Hesperidin	-8.5	-7.1	-6.3	-6.6	-6.3	-6.9	-8.2	-6.4
Rosmarinic Acid	-8.0	-6.0	-6.2	-6.6	-5.6	-7.5	-7.3	-5.6
Withaferine A	-8.5	-8.8	-8.7	-8.2	-7.0	-8.1	-9.2	-7.1

Table 3. Auto-Dock Vina Binding Affinities ΔG (kcal/mol) – Targets 9-15

Compound	MAPK3	MAPK8	MAPK10	MMP2	STAT3	STAT1	TNF	Mean ΔG
Apigenin	-7.7	-7.5	-7.0	-8.8	-6.6	-6.8	-5.4	-8.60
Berberine	-7.3	-7.4	-7.5	-8.2	-6.0	-7.0	-5.5	-8.55
Fisetin	-7.6	-7.5	-7.2	-9.0	-7.5	-6.6	-6.3	-8.95
EGCG	-8.5	-8.0	-7.5	-7.9	-6.3	-7.3	-5.3	-8.72
Palmatine	-6.7	-7.1	-7.0	-7.1	-5.2	-6.4	-5.1	-7.60
Hesperidin	-7.7	-7.5	-7.0	-9.2	-6.6	-6.8	-5.5	-8.63
Rosmarinic Acid	-7.0	-7.1	-6.1	-8.9	-6.9	-6.1	-5.2	-8.45
Withaferine A	-8.7	-8.5	-8.2	-8.2	-7.4	-7.8	-5.6	-8.51

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FIGURE LEGENDS

Figure 1. MolSoft drug-likeness analysis of selected phytoconstituents.

Figure 2. SwissTargetPrediction-derived molecular targets of selected phytoconstituents. Figure 3. GeneCards-derived disease-associated targets related to gut–brain axis inflammation.

Figure 4. VarElect-based prioritization of common targets according to disease relevance scores. Figure 5. STRING protein–protein interaction network of prioritized inflammatory targets.

Figure 6. Cytoscape-based compound–target interaction network.

Figure 7. KEGG MAPK signaling pathway enrichment analysis of prioritized targets.

Figure 8. Representative molecular docking interactions of selected phytoconstituents with prioritized inflammatory targets.

Figure 9. Computational meta-analysis comprising heatmap visualization, hierarchical clustering, Pearson correlation analysis, radar plot comparison, and compound–target interaction profiling of selected phytoconstituents.

FIGURES

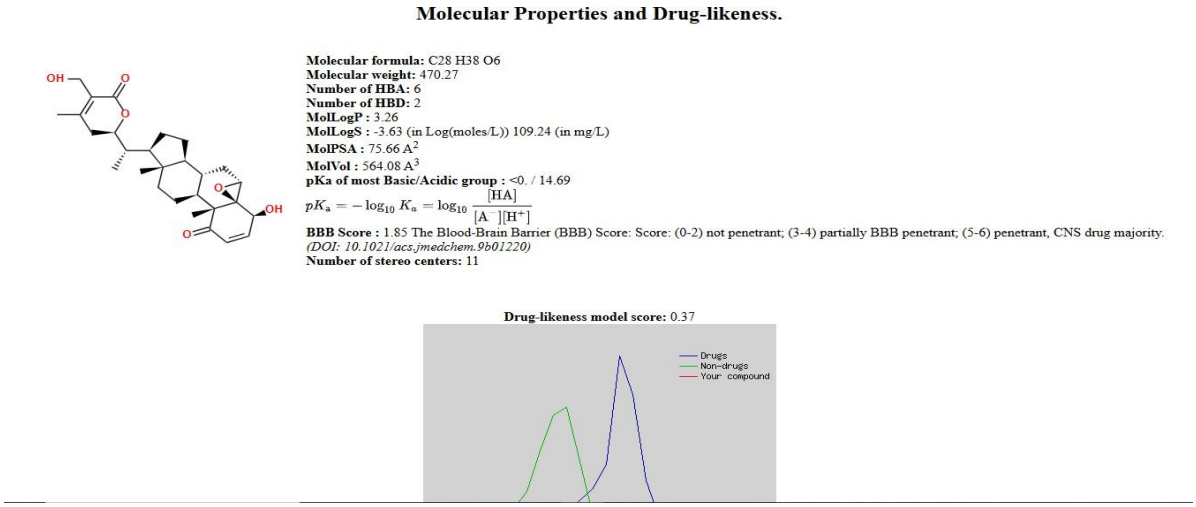

Figure 1

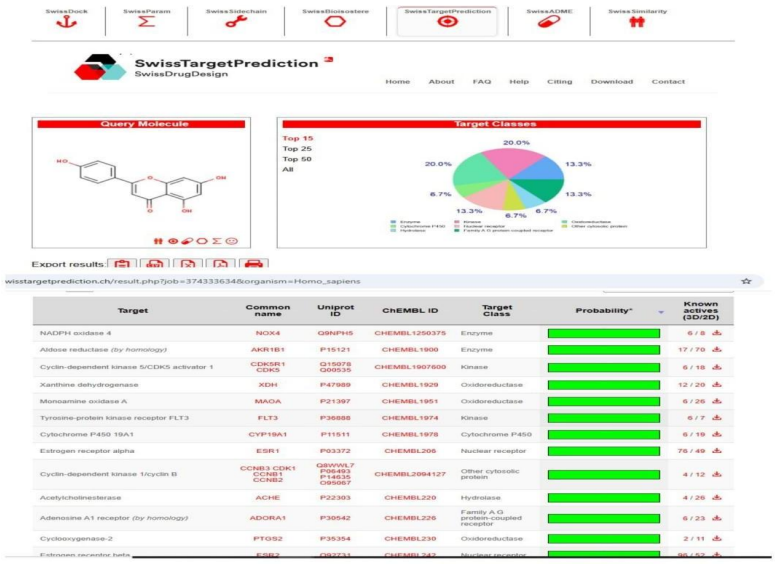

Figure 2

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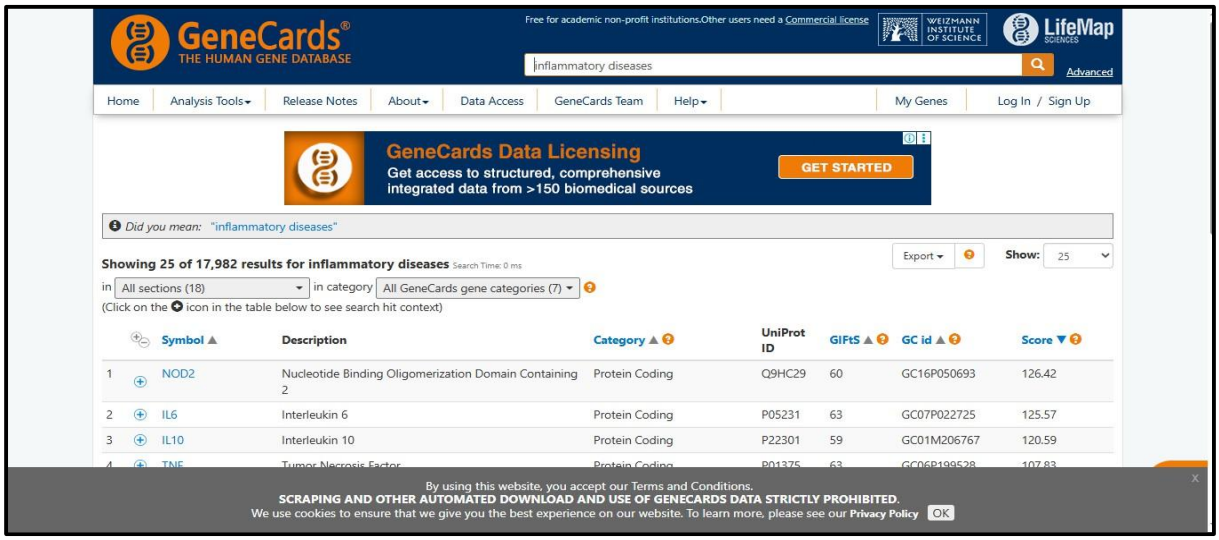

Figure 3

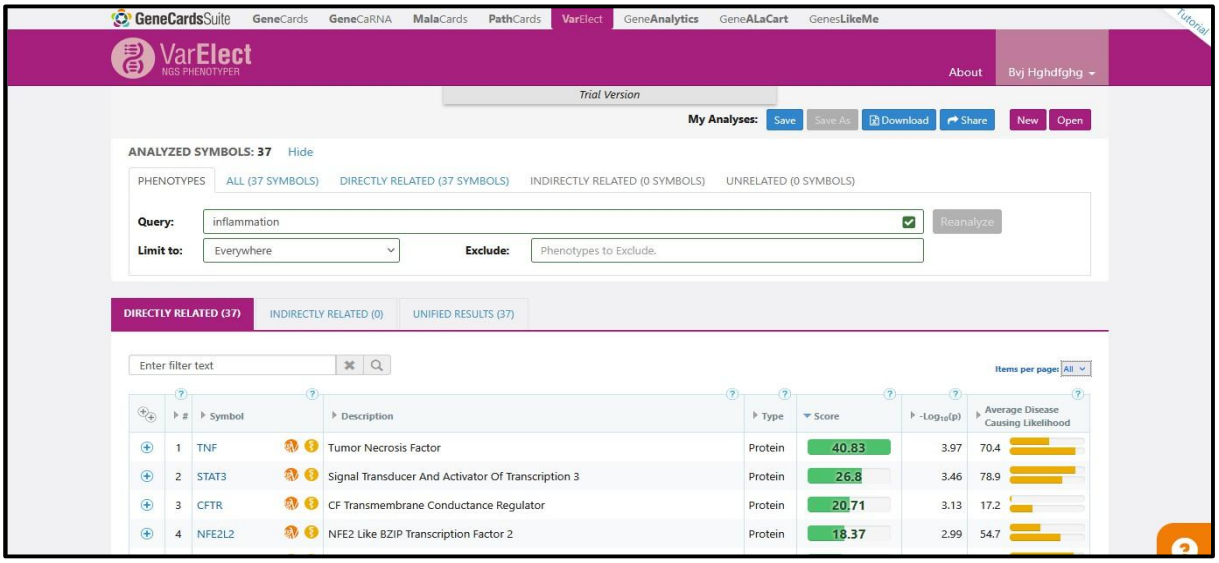

Figure 4

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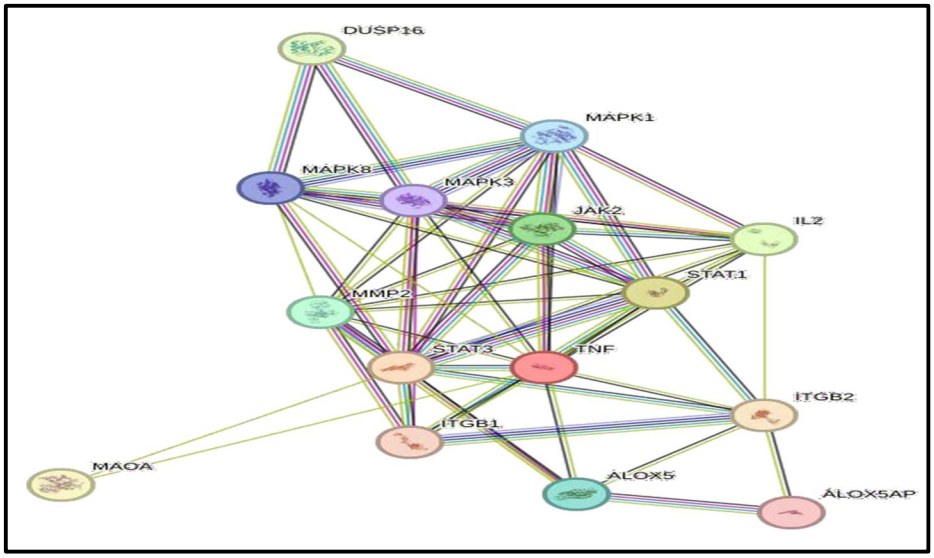

Figure 5

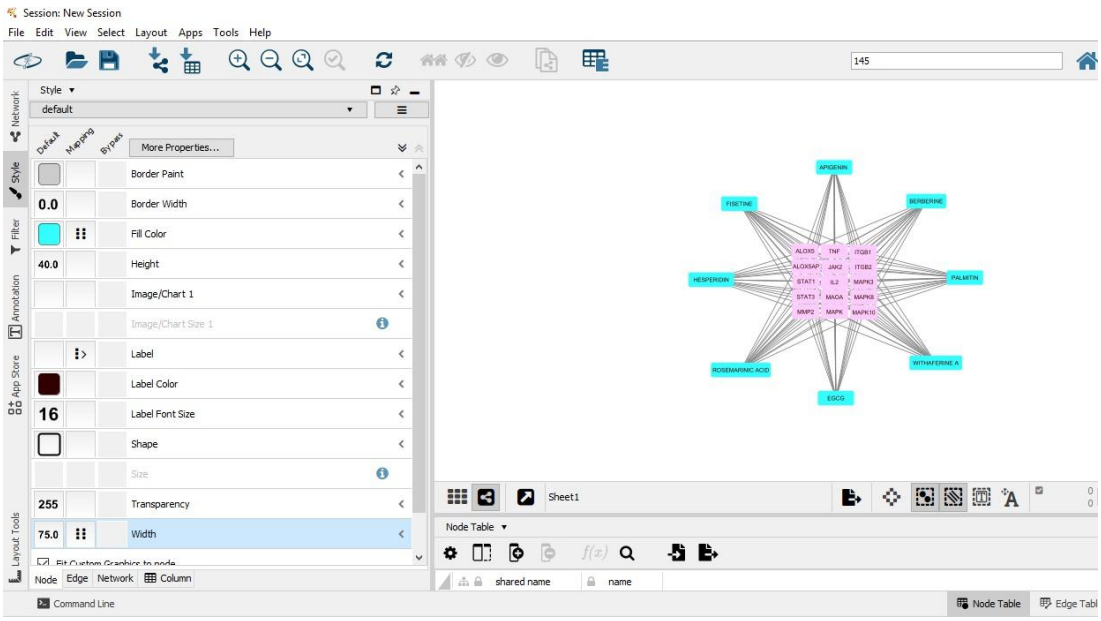

Figure 6

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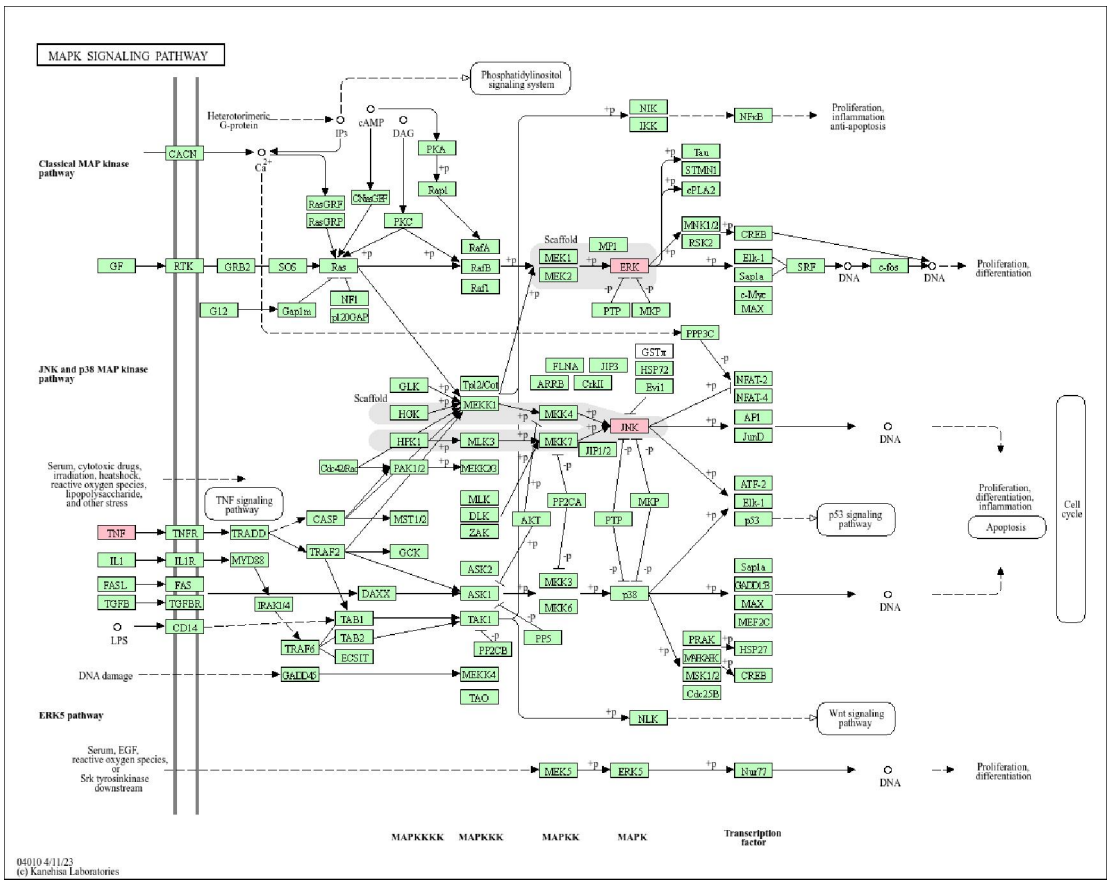

Figure 7

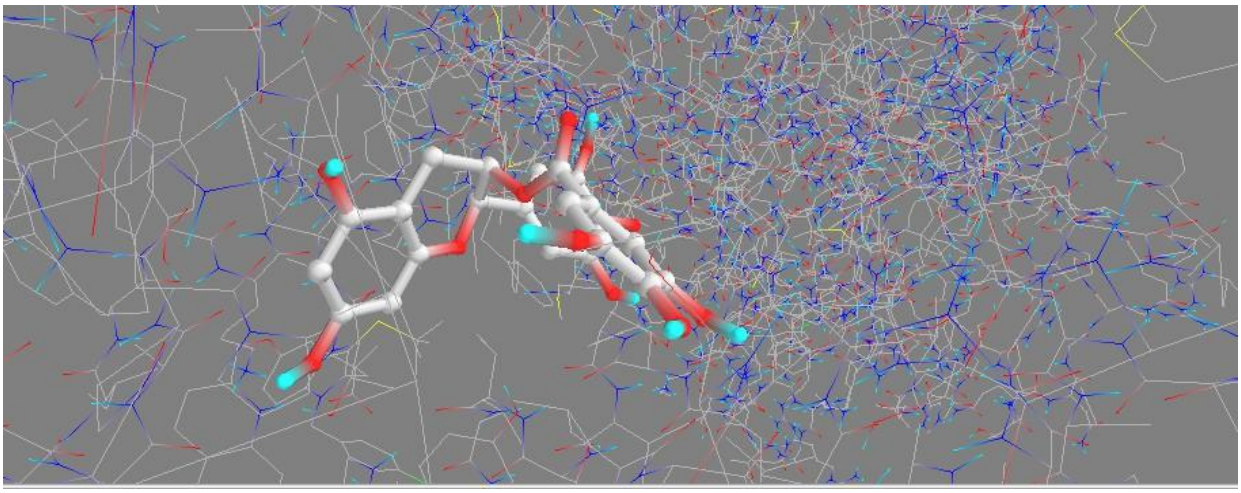

Figure 8

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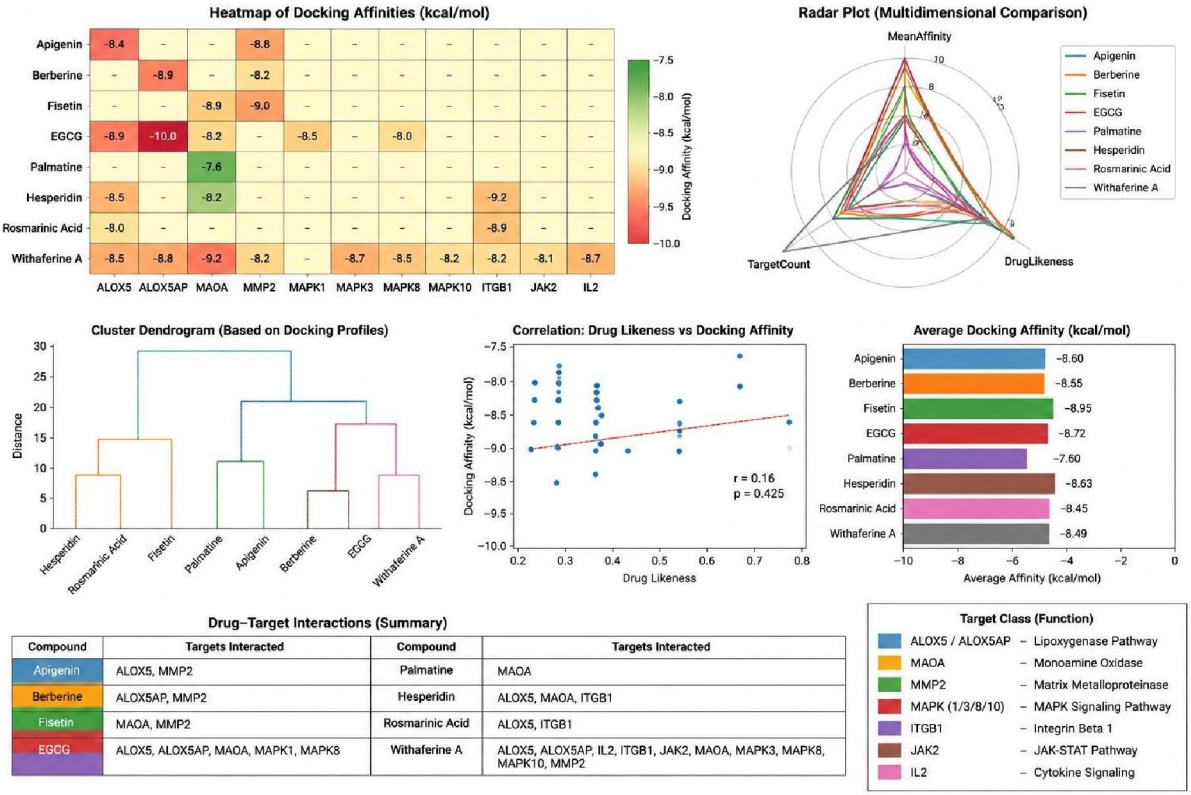

Drug–Target Interactions (Summary)

Compound	Targets Interacted	Compound	Targets Interacted
Apigenin	ALOX5, MMP2	Palmatine	MAOA
Berberine	ALOX5AP, MMP2	Hesperidin	ALOX5, MAOA, ITGB1
Fisetin	MAOA, MMP2	Rosmarinic Acid	ALOX5, ITGB1
EGCG	ALOX5, ALOX5AP, MAOA, MAPK1, MAPK8	Withaferine A	ALOX5, ALOX5AP, IL2, ITGB1, JAK2, MAOA, MAPK3, MAPK8, MAPK10, MMP2

Target Class (Function)

ALOX5 / ALOX5AP	Lipoxygenase Pathway
MAOA	Monoamine Oxidase
MMP2	Matrix Metalloproteinase
MAPK (1/3/8/10)	MAPK Signaling Pathway
ITGB1	Integrin Beta 1
JAK2	JAK-STAT Pathway
IL2	Cytokine Signaling

Figure 9

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