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ANALYSIS OF THE POTENTIAL MECHANISM OF CHLOROGENIC ACID IN THE TREATMENT OF SEPSIS BASED ON MULTIDIMENSIONAL BIOINFORMATICS

Yufei Lu, Tingting Fu, Xinna Li, Wenqian Wang, Xueru Huang, Qinghui Sun*

National Health Commission Key Laboratory of Control of Tropical Diseases, School of Life Sciences and Medical Technology, Hainan Medical University, Haikou, Hainan 571199, China

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Corresponding author: Qinghui Sun

ABSTRACT

Using multi-dimensional bioinformatics, this study systematically explores the immunomodulatory mechanisms of chlorogenic acid (CGA) in sepsis. By integrating five databases, we identified 337 putative targets; Disease Ontology (DO), Gene Ontology (GO), and KEGG pathway analyses indicated primary involvement in oxidative stress, immune regulation, and cellular repair pathways. Transcriptomic profiling revealed 13,509 differentially expressed genes, and weighted gene co-expression network analysis (WGCNA) uncovered modules closely associated with sepsis, enriched for macrophage activation and monocyte chemotaxis. An integrative analysis further pinpointed 53 key genes implicated in neutrophil extracellular trap (NET) formation, necroptosis, and Fcγ receptor–mediated phagocytosis. Immune infiltration analysis suggested upregulation of pro-inflammatory genes in neutrophils, while molecular docking indicated that CGA can stably bind to key proteins such as TNF, IL1B, and MMP9. Although these findings suggest a potential immunomodulatory role for CGA in sepsis, additional experimental studies are required to validate its therapeutic value.

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INTRODUCTION

Sepsis is a life-threatening condition caused by a dysregulated host response to infection, exhibiting exceptionally high morbidity and mortality rates. Globally, it affects more than 48 million people annually and leads to approximately 11 million deaths [1]. The clinical course is characterized by systemic inflammation, microcirculatory dysfunction, and multiple organ failure; moreover, survivors frequently suffer from immunosuppression and a diminished quality of life, underscoring the urgent need for effective therapeutic strategies. Current clinical management primarily relies on supportive care, pathogen eradication, and immunomodulation. Although antibiotics remains the cornerstone of treatment, the emergence of multidrug-resistant pathogens significantly diminishes its efficacy. Furthermore, these agents do not fundamentally address the underlying pathophysiological mechanisms of sepsis. Chlorogenic acid (CGA), a natural polyphenol, possesses multi-target activities including anti-inflammatory, antioxidant, and immunomodulatory effects[3-4]. CGA exhibits potential in intervening in the pathological processes of sepsis by modulating the NF-κB/MAPK pathways, inhibiting pro-inflammatory cytokines, enhancing the expression of anti-inflammatory factors, and restoring immune balance [4-5]. This study aims to systematically analyze the mechanisms of CGA in regulating inflammation, oxidative stress, and immune responses. By filling existing therapeutic gaps and leveraging the multi-target properties of CGA, we hope to provide novel intervention strategies and therapeutic insights for this complex and highly lethal syndrome.

METHODS

Acquisition of drug target genes: To identify the potential molecular targets of chlorogenic acid (CGA) in sepsis, we retrieved target genes from four public databases: BindingDB, SwissTargetPrediction, CTD, and TargetNet. We subsequently constructed a Venn diagram to identify overlapping genes, which were defined as high-confidence targets. To elucidate their functional significance, we performed Disease Ontology (DO), Gene Ontology (GO), and KEGG pathway enrichment analyses using the DOSE, clusterProfiler, and org.Hs.eg.db packages. Furthermore, we extracted the standardized SMILES structure of CGA from PubChem to support subsequent structural and interaction analyses [6].

Weighted Gene Co-expression Network Analysis (WGCNA): To identify key gene modules associated with sepsis and potentially serving as targets for CGA, we performed Weighted Gene Co-expression Network Analysis (WGCNA) on the transcriptomic dataset GSE232753. Prior to analysis, we normalized the data, removed low-variance genes, and excluded outlier samples via hierarchical clustering to ensure network stability. We identified modules using the dynamic tree cut method and assessed their correlation with clinical phenotypes (sepsis vs. normal) using Pearson correlation coefficients. We defined modules showing a high positive correlation with sepsis as "key modules." Furthermore, we calculated

module membership (MM) and gene significance (GS) to confirm a significant correlation between them.

Enrichment Analysis: We performed GO and KEGG enrichment analyses on the predicted drug targets and genes within the WGCNA key modules using the clusterProfiler package to systematically evaluate their biological functions and pathway involvement.

Correlation Analysis: Between Immune Infiltration Scores and Gene Expression Levels We cleaned the column names ending in "_CIBERSORT" in the immune infiltration data and retained only immune cell types with $p < 0.05$ for analysis. We filtered the key genes listed in keycluster.txt from the gene expression matrix and extracted samples shared with the immune data. We employed Spearman correlation coefficients to assess the correlation between various immune cell subtypes and key gene expression levels, calculating p-values using the cor.test() function. We utilized ggplot2 to generate correlation heatmaps, visualizing the pairwise relationships between genes and immune cells.

Molecular Docking Analysis: To analyze the molecular interactions between chlorogenic acid (CGA) and six sepsis-related target proteins (CASP8, EGFR, IL1B, MAPK8, MMP9, and TNF), we conducted molecular docking using AutoDock Vina. We obtained the three-dimensional (3D) structures of the target proteins from the RCSB PDB; prior to docking, we removed water molecules and added hydrogen atoms to optimize ligand binding. We optimized the 3D structure of CGA using ChemDraw and converted it into the PDBQT format. We set the grid parameters based on the global protein structure to define the binding pocket range. The docking process was based on the Lamarckian genetic algorithm of AutoDock Vina, running with default parameters. We visualized the docking results using PyMOL and LigPlot+ to analyze key interactions, such as hydrogen bonding, hydrophobic, and electrostatic interactions between CGA and the target proteins.

RESULTS

Identification of Chlorogenic Acid-related Targets and Pathways in Sepsis: We identified drug target genes related to chlorogenic acid (CGA) across five databases, including BindingDB (n=6), SwissTargetPrediction (n=100), Comparative Toxicogenomics Database (CTD, n=194), and TargetNet (n=102) (Figure 1A). To define the functional relevance of these target genes, we conducted Disease Ontology (DO), Gene Ontology (GO), and KEGG pathway enrichment analyses (Figure 1B-D). DO analysis revealed that CGA target genes significantly participate in diseases associated with the systemic inflammatory response characteristic of sepsis, such as cardiovascular, hepatic, renal, and respiratory disorders (Figure 1B). KEGG analysis further demonstrated that these genes are involved in key pathways, including oxidative stress regulation, immune response modulation, and cellular repair mechanisms (Figure 1C). GO enrichment analysis indicated that CGA target genes are significantly enriched across three dimensions: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF), further supporting their potential in sepsis treatment (Figure 1D).

Differential Expression and Pathway Enrichment Analysis of Chlorogenic Acid Target Genes: We performed normalization and variance analysis on the RNA microarray data from sepsis samples, identifying 13,509 differentially expressed genes (DEGs) ($logFC > 0.01$, $P < 0.05$). Among these, we found 13 genes to be downregulated, while the remainder were upregulated (Figure 2A). The heatmap visualizes the expression patterns of the primary DEGs in the normal and sepsis groups, revealing distinct clustering differences and reflecting specific target genes potentially regulated by chlorogenic acid in sepsis (Figure 2B). Gene Set Enrichment Analysis (GSEA) demonstrated that the downregulated pathways primarily involve immune dysregulation and inflammatory responses, such as "Complement and coagulation cascades,""Leukocyte

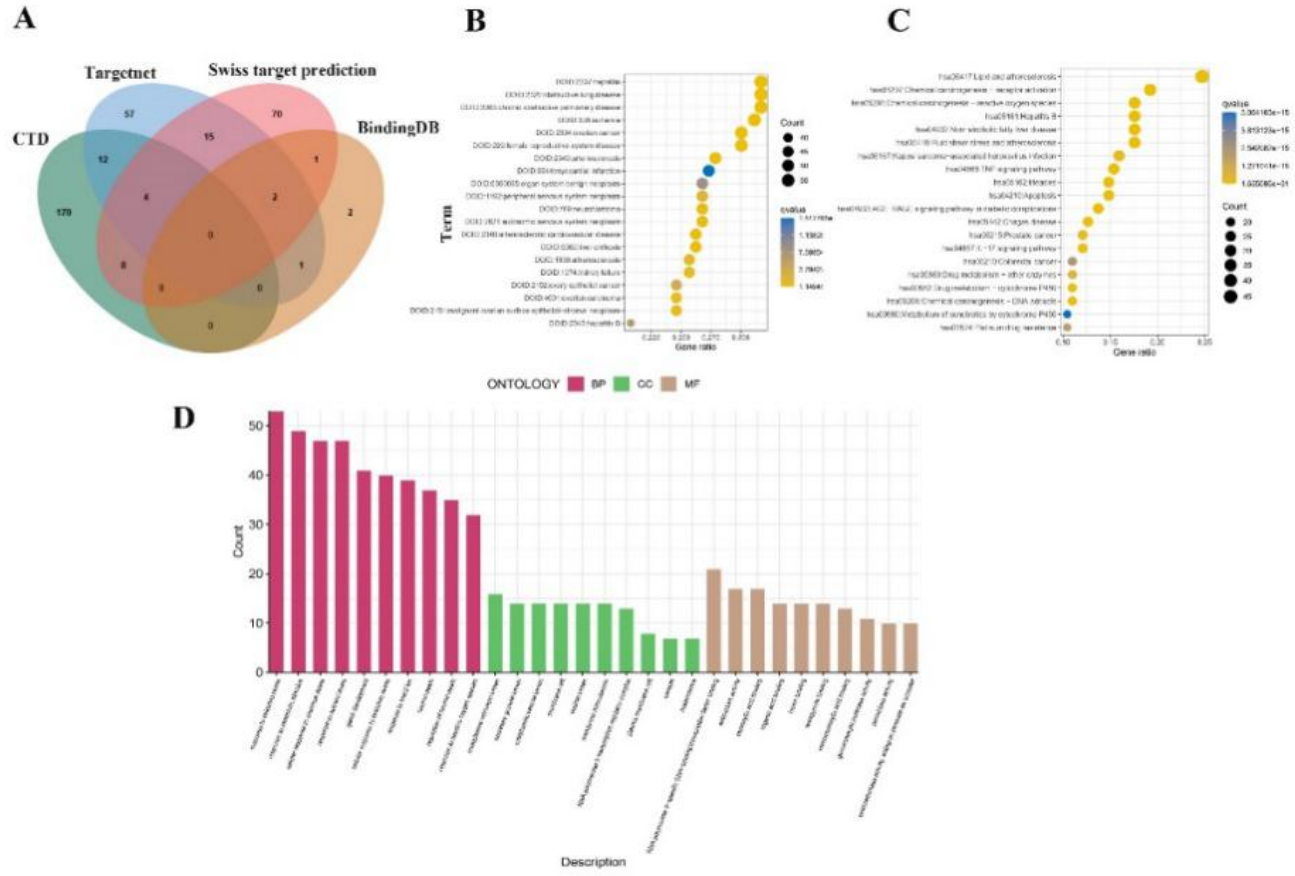

Figure 1. Analysis of drug target genes. (A) Target overlap analysis; (B) Disease Ontology (DO) analysis; (C) KEGG pathway enrichment analysis; (D) Gene Ontology (GO) analysis

transendothelial migration,""Neutrophil extracellular trap formation," and "Type 1 diabetes mellitus" (Figure 2C). In contrast, the upregulated pathways included "Allograft rejection,""Activated immune response," and "Graft-versus-host disease," suggesting their association with the immune activation process in sepsis (Figure 2D).

Key Gene Sets and Pathway Analysis: The Venn diagram showed 53 overlaps between the 4,607 genes obtained from WGCNA and the 392 genes identified via differential expression analysis (Figure 3A). GO enrichment analysis indicated that these overlapping genes participate in biological processes such as "macrophage

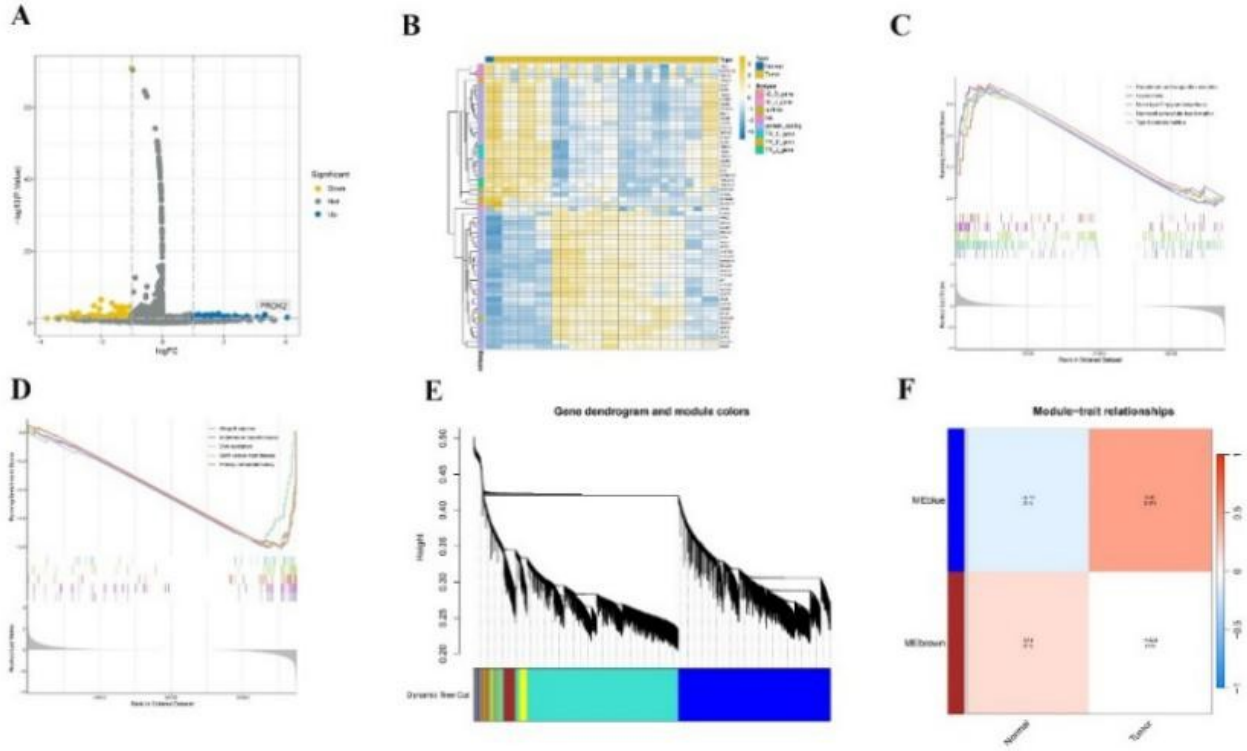

Figure 2. Differential gene expression analysis in sepsis. (A) Volcano plot of differentially expressed genes (DEGs); (B) Heatmap of differentially expressed genes across samples; (C) GSEA analysis of downregulated pathways; (D) GSEA analysis of upregulated pathways; (E) Gene clustering dendrogram and module identification; (F) Correlation analysis between modules and phenotypes

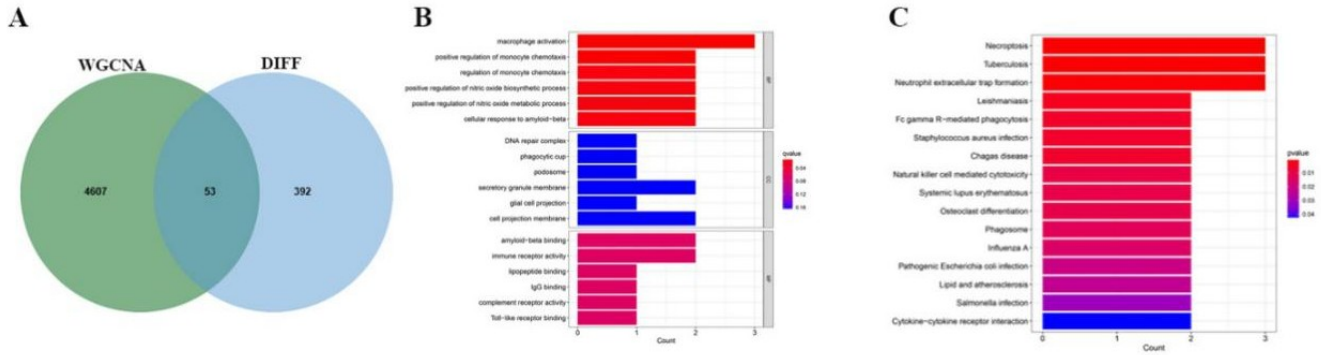

Figure 3. Identification of Key Gene Sets and Pathway Analysis. (A) Overlap analysis between WGCNA gene modules and differentially expressed genes (DEGs); (B) GO enrichment analysis of the overlapping genes; (C) Network analysis of KEGG pathways

Weighted Gene Co-expression Network Analysis (WGCNA) of Chlorogenic Acid Target Genes:To further explore the mechanisms of chlorogenic acid in sepsis, we applied WGCNA to the GSE232753 dataset. We selected a soft-thresholding power of 12 to optimize the scale-free topology fitting index ($R^2 \approx 0.9$), ensuring the robustness of the network construction. Hierarchical clustering analysis revealed distinct grouping differences between the normal and sepsis samples; significant correlations between each co-expression module and clinical traits emphasized their potential roles in the pathogenesis of sepsis (Figure 2C). The dynamic tree cut algorithm identified the "blue module" as having the strongest correlation with sepsis traits, suggesting this module plays a pivotal role in disease progression (Figure 2D). The strong correlation between module membership (MM) and gene significance (GS) further validated the biological importance of the genes within this module under sepsis conditions (Figures 2E, F).

activation,""positive regulation of monocyte chemotaxis," and "phagosome formation," as well as molecular functions including "amyloid-beta binding" and "immune receptor activity" (Figure 3B). The bar chart illustrates the KEGG pathway enrichment results, where pathways such as "necroptosis,""tuberculosis," and "neutrophil extracellular trap formation" exhibited significant enrichment (Figure 3C).

Analysis of Chlorogenic Acid-related Disease Genes: The Venn diagram identified 5 overlapping genes between chlorogenic acid target genes (n=337) and sepsis-related genes (n=49) (Figure 4A). Network analysis of CGA-related targets revealed several hub genes that play crucial roles within the network; the overlapping genes include AKT1, IL1B, EGFR, IL6, and TNF, all of which are key regulators in immunity and inflammation (Figure 4B). KEGG enrichment analysis demonstrated that these genes participate in

inflammation-related pathways such as the "IL-17 signaling pathway,""TNF signaling pathway," and "Toll-like receptor signaling pathway" (Figure 4C). GO analysis further indicated that these genes involve biological processes such as "response to mechanical stimulus,""myeloid leukocyte differentiation," and "response to cellular oxidative stress" (Figure 4D).

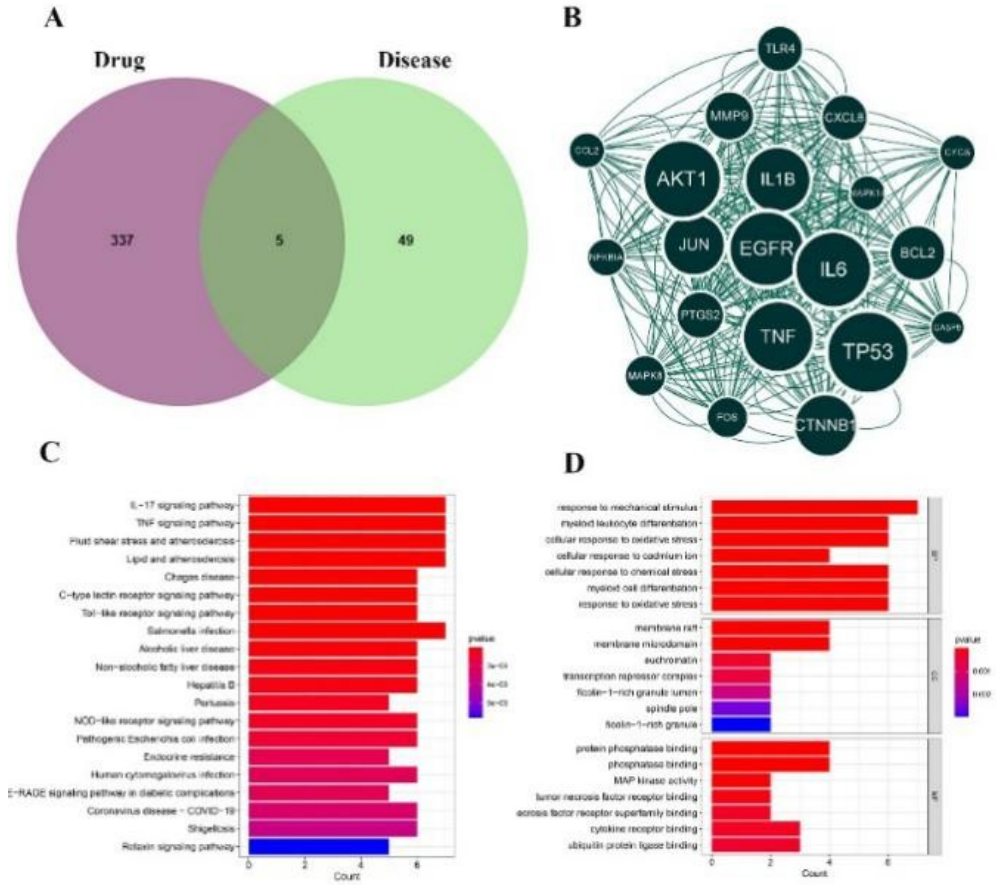

Figure 4. Analysis of chlorogenic acid (CGA) related genes. (A) Common target genes between CGA and sepsis; (B) PPI network of the overlapping genes; (D) Pathway enrichment analysis of the overlapping genes; (E) GO enrichment analysis of the overlapping genes

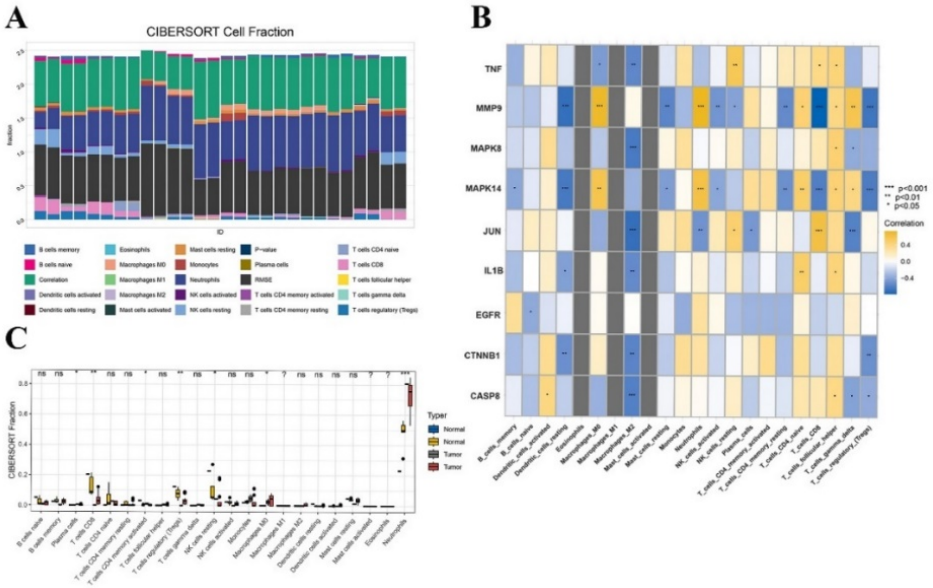

Figure 5. Changes in immune cell composition. (A) Immune cell composition; (B) Heatmap of key genes associated with immune cell composition; (C) Quantitative analysis of immune cell composition in normal and sepsis samples

Immune Landscape of Sepsis and the Impact of Chlorogenic Acid : CIBERSORT analysis revealed significant alterations in the immune cell composition of sepsis samples, with the most prominent changes occurring in macrophages, neutrophils, and T cells. In the sepsis group, the proportions of activated macrophages and neutrophils increased significantly, indicating their central role in driving inflammation; meanwhile, regulatory T cells (Tregs) and certain memory T cell subsets decreased significantly, suggesting an immunosuppressive tendency (Figure 5A). The correlation heatmap showed that pro-inflammatory factors, including TNF, MMP9, and IL1B; conversely, anti-inflammatory factors such as CTNNB1 correlated negatively with these cells(Figure 5B) and macrophages were significantly enriched in the sepsis group ($p < 0.05$), aligning with the acute inflammatory state of sepsis (Figure 5C).

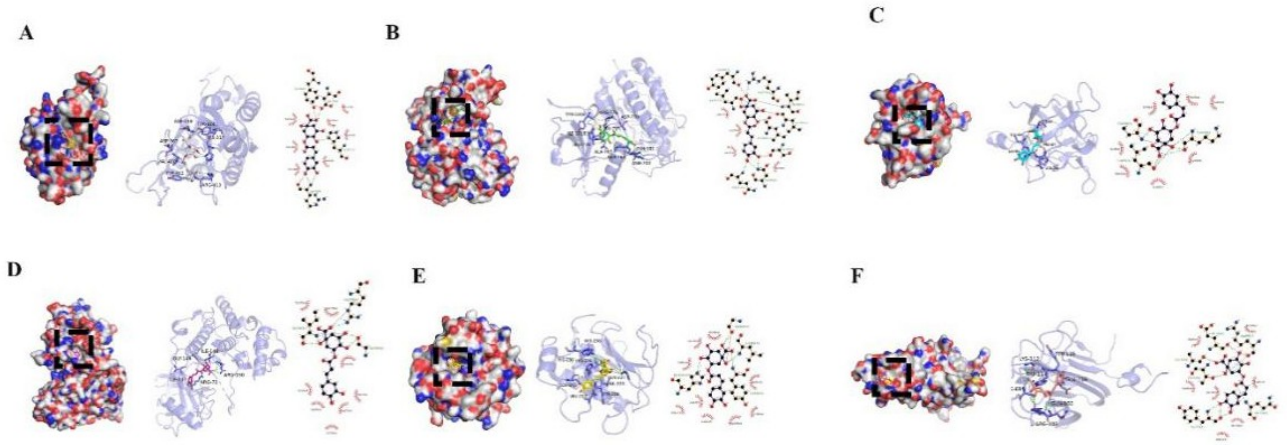

Figure 6. Molecular docking analysis of protein-ligand interactions. (A) Docking model of CASP8 with chlorogenic acid; (B) Docking model of EGFR with chlorogenic acid; (C) Docking model of IL1B with chlorogenic acid; (D) Docking model of MAPK8 with chlorogenic acid; (E) Docking model of MMP9 with chlorogenic acid; (F) Docking model of TNF with chlorogenic acid. Each panel displays the electrostatic surface (left), ribbon structure (middle), and a 2D diagram illustrating molecular interactions (right) of the protein-ligand complex

Molecular Docking Analysis of Key Genes in Sepsis Pathways with Chlorogenic Acid: Chlorogenic acid (CGA) exhibited strong binding affinity with all six target proteins, showing low binding free energy values ranging from -7.2 to -9.8 kcal/mol (Figure 6). CGA interacted strongly with CASP8, forming two key hydrogen bonds with Asp313 (2.8 Å) and Thr312 (3.1 Å). The primarily hydrophilic binding pocket of CASP8 allowed the hydroxyl groups of CGA to establish stable polar interactions (Figure 6A). In Epidermal Growth Factor Receptor (EGFR), CGA formed stable hydrogen bonds with Tyr308 (2.9 Å) and Ala767 (3.0 Å). Furthermore, the π-π stacking interaction between the aromatic ring of CGA and Tyr308 enhanced the overall binding stability. The partially hydrophobic binding pocket accommodated the aromatic scaffold of CGA (Figure 6B). Regarding IL1B, CGA established hydrogen bonds with Cys116 (2.7 Å) and Tyr114 (3.2 Å) and exhibited significant hydrophobic interactions with adjacent residues such as Val110 and Leu113. The carboxyl group of CGA played a pivotal role in anchoring the molecule within the binding cleft (Figure 6C). In the case of MAPK8, CGA formed strong electrostatic interactions with Glu134 and Arg150, alongside hydrogen bonds of 2.8 Å and 3.0 Å. MMP9 primarily interacted with CGA through hydrophobic forces, with Lys222 and His230 providing key anchor points. A 2.9 Å hydrogen bond with Lys222 further stabilized the interaction. The hydrophobicity of the binding pocket favored the accommodation of the aromatic moiety of CGA (Figure 6E). Finally, TNF exhibited strong interaction with CGA, forming hydrogen bonds with Arg103 (3.0 Å) and Cys69 (3.1 Å). The phenolic hydroxyl groups of CGA contributed significantly to these interactions, stabilizing the complex within a binding pocket characterized by both hydrophilic and hydrophobic properties (Figure 6F).

CONCLUSION

Chlorogenic acid (CGA) demonstrates significant potential as a therapeutic agent for sepsis by multidimensionally regulating immune responses, inflammation, and cellular repair processes. CGA targets key proteins and signaling pathways, such as the TNF signaling pathway, neutrophil extracellular trap formation, and macrophage activation, to effectively balance pro-inflammatory and anti-inflammatory responses in sepsis. Molecular docking results further confirm that CGA exhibits favorable binding affinities with several key sepsis-related proteins, suggesting its promising application in drug development. These findings establish a solid foundation for future exploration of the mechanisms of chlorogenic acid in sepsis treatment and its application in a broader range of inflammatory diseases.

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