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Unraveling the Nephroprotective Potential of *Curcuma zedoaria* Against Chronic Kidney Disease: A Network Pharmacology Approach

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ABSTRACT: *Chronic kidney disease (CKD) remains a major global health concern with limited treatment options. Curcuma zedoaria, a traditional medicinal plant, has shown potential in managing inflammatory and oxidative stress-related conditions. This study aimed to explore its nephroprotective mechanisms through a network pharmacology approach. A total of 12 bioactive compounds were identified from C. zedoaria and screened for drug-likeness. SwissTargetPrediction revealed multiple molecular targets, with curdione, dehydrocurdione, and curcumin showing the highest connectivity. Integration with CKD-associated genes from GeneCards and GSE66494 datasets yielded 241 common targets. Using Cytoscape, a compound–target–disease network was constructed, highlighting key biological processes such as inflammation, apoptosis, and fibrosis. PPI analysis identified top hub proteins including HSP90AA1, STAT3, SRC, AKT1, MAPK1, and MAPK3. Functional enrichment via GO and KEGG pathways revealed significant involvement of EGFR tyrosine kinase inhibitor resistance and HIF-1 signaling pathways. These findings suggest that C. zedoaria exerts protective effects through a multitarget mechanism modulating critical pathways in CKD progression. This study provides a theoretical basis for further experimental validation and supports the potential use of C. zedoaria as a complementary therapy in CKD management.*

Keywords: *chronic kidney disease; curcuma zedoaria; functional enrichment analysis; hub targets; network pharmacology*

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1. Introduction

Chronic kidney disease (CKD) represents a major global public health challenge, affecting approximately 10% of the world population. It is defined as abnormalities in kidney structure or function that persist for more than three months, with implications for long-term health outcomes [1]. CKD progresses silently and is often associated with comorbidities such as diabetes mellitus, hypertension, and cardiovascular diseases [2]. The progressive loss of renal function leads to the accumulation of metabolic waste products, electrolyte imbalance, and systemic inflammation, which further exacerbate tissue damage and organ dysfunction [3]. Despite significant advancements in medical care, current therapeutic strategies primarily aim at managing symptoms and delaying disease progression rather than offering curative solutions [1]. Hence, there is a pressing need to explore novel therapeutic agents particularly those derived from natural sources that can target multiple pathological pathways simultaneously with minimal side effects.

In recent decades, there has been a resurgence of interest in traditional medicinal systems due to their holistic approach to disease management [4]. These systems emphasize the use of plant-based formulations that exert their effects through modulation of multiple biological targets, aligning well with the complex etiology of chronic diseases like CKD. Among the numerous medicinal plants studied for their therapeutic potential, *Curcuma zedoaria*, commonly known as zedoary, stands out due to its wide array of pharmacological activities, including anti-inflammatory, antioxidant, antifibrotic, and immunomodulatory effects [5–7]. While traditionally used for digestive ailments and inflammatory conditions, emerging evidence suggests that *C. zedoaria* may also offer chronic kidney disease, functional enrichment analysis, hub targets, network pharmacology protection against organ-specific injuries, including those affecting the kidneys [7].

The therapeutic potential of *C. zedoaria* stems from its rich phytochemical profile, which includes sesquiterpenes, curcuminoids, flavonoids, and other bioactive compounds. Notable among these are germacrone, curzerene, furanodiene, and β-elemene, which have demonstrated protective effects in various experimental models of oxidative stress and inflammation [7]. Oxidative stress and chronic inflammation are key drivers in the pathogenesis of CKD, contributing to glomerular hyperfiltration, podocyte injury, tubulointerstitial fibrosis, and endothelial dysfunction [8]. The ability of *C. zedoaria* constituents to modulate redox-sensitive signaling pathways such as Nrf2/Keap1 and NF-κB, along with their capacity to inhibit pro-inflammatory cytokines and matrix metalloproteinases, makes this plant a promising candidate for nephroprotection [9]. However, despite several experimental studies suggesting its renal protective effects, the molecular mechanisms behind these actions remain poorly characterized.

One of the major challenges in understanding the therapeutic effects of herbal medicines lies in their complexity: they typically contain dozens of bioactive components, each capable of interacting with multiple molecular targets [10]. This polypharmacological nature cannot be adequately addressed by conventional single-target drug discovery approaches. To overcome this limitation, network pharmacology has emerged as a powerful interdisciplinary tool that integrates systems biology, computational modeling, and pharmacoinformatics to unravel the intricate interactions between drugs, targets, and diseases [11]. By constructing multi-layered networks, such as compound-target, target-disease, and protein-protein interaction (PPI) networks—network pharmacology allows researchers to identify core regulatory nodes and functional pathways involved in drug action, providing mechanistic insights that guide hypothesis-driven experimental validation.

This study aims to bridge this knowledge gap by conducting a systematic network pharmacology-based analysis of *C. zedoaria* in the context

of chronic kidney disease. We employed a multi-disciplinary approach involving the identification of bioactive compounds, prediction of potential therapeutic targets, integration with CKD-related genes, construction of interaction networks, and functional enrichment analysis. Through this integrative strategy, we sought to uncover the molecular underpinnings of *C. zedoaria* -mediated nephroprotection, identify key hub targets, and map the most relevant biological pathways involved in its therapeutic mechanism. Our findings are expected to provide a theoretical framework for future in vitro and in vivo studies, laying the groundwork for the development of herbal-derived therapeutics targeting multiple aspects of CKD pathology.

2. Methods

2.1. Collection of bioactive compounds in C. zedoaria

Bioactive compounds present in *C. zedoaria* were systematically retrieved from the Dr. Duke's Phytochemical and Ethnobotanical Databases (https://phytochem.nal.usda.gov/), a comprehensive and publicly accessible resource containing detailed information on plant-derived chemical constituents and their associated biological activities. A search was conducted using the full scientific name *C. zedoaria* to obtain all reported compounds. To ensure relevance for pharmacological investigation, only naturally occurring compounds with confirmed presence in the plant and documented evidence of biological activity were selected. Compounds lacking experimental validation or those identified as synthetic derivatives were excluded from further analysis. In addition, to prioritize compounds with potential therapeutic value, a bioactivity count filter was applied, retaining only those associated with at least one recorded biological effect. Additionally, the pkCSM server (http://biosig.unimelb.edu.au/pkcsm) was employed to evaluate the pharmacokinetic properties of the selected compounds [12]. Those fulfilling Lipinski's Rule of Five including molecular weight ≤ 500 Da, LogP ≤ 5, hydrogen bond donors ≤ 10, and hydrogen bond acceptors ≤ 5 were considered drug-likeness and were retained for subsequent target prediction and network analysis. This multi-step screening process ensured that only naturally derived, bioactive, and pharmacokinetically favorable compounds were advanced for further investigation, enhancing the likelihood of identifying therapeutically relevant candidates involved in nephroprotection.

2.2. Target prediction and construction of compound-target-disease network

Potential molecular targets of the identified *C. zedoaria* compounds were predicted using the SwissTargetPrediction server (http://www.swisstargetprediction.ch/), which employs ligand-based similarity methods to forecast interactions between small molecules and protein targets [13]. Only predictions with a probability score >0 were considered reliable and were selected for further processing [14,15]. The potential targets of from compounds of *C. zedoaria* and thiers targets with disease were constructed by Cytoscape 3.10.3 [16].

2.3 Identification of chronic kidney disease (CKD)-related genes

To establish a disease-specific target profile, genes linked to chronic kidney disease were obtained from the GeneCards database (https://www.genecards.org/), which aggregates gene-disease associations from multiple authoritative sources [17]. A keyword-based search using "chronic kidney disease" was performed and to enhance specificity and ensure compatibility with pharmacological and network analyses, only genes encoding protein-coding sequences were retained. Non-protein-coding elements such as long non-coding RNAs, microRNAs, and pseudogenes were systematically removed from the dataset. The final list of protein-coding CKD-related genes was used for downstream

integration with compound targets.

2.4 Screening of differentially expressed genes (DEGs) from GSE66494 dataset

To identify gene expression changes relevant to CKD pathology, we analyzed the GSE66494 microarray dataset from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/), which contains transcriptomic profiles from renal biopsy samples of CKD patients and healthy controls [18]. Differential gene expression analysis was performed using the R/Bioconductor package 'limma'. Genes showing statistically significant differences were defined by thresholds of adjusted p-value < 0.05 and log2 fold change > 1 [19]. These differentially expressed genes (DEGs) were then integrated with the previously compiled list of CKD-related protein-coding genes to refine the disease-associated target pool.

2.5 Protein-protein interaction (PPI) network construction and hub target identification

To further explore functional relationships among the shared therapeutic targets of *C. zedoaria* and CKD identified through Venn diagram analysis, a PPI network was constructed. The intersected target list comprising CKD-associated genes obtained from GeneCards and differentially expressed genes from the GSE66494 dataset, along with compound-related targets was uploaded to the STRING database (v12) [20]. Only interactions corresponding to Homo sapiens were selected, with a minimum confidence score of 0.9 to ensure high reliability of predicted interactions [21]. The resulting PPI network was exported in TSV format and imported into Cytoscape v3.10.3 for visualization and topological analysis. Within Cytoscape, the CytoHubba plugin was utilized to identify key hub targets based on number of degree, a measure of the number of interactions per node within the network [22]. The top ten targets with the highest degree values were considered as central regulatory nodes likely involved in mediating the nephroprotective effects of *C. zedoaria*. This approach facilitated the identification of potential key molecular players and provided insights into the multi-target mechanisms underlying the plant's therapeutic activity in CKD.

2.6 Functional enrichment analysis

To elucidate the biological functions and pathways associated with the shared therapeutic targets identified through Venn diagram analysis, functional enrichment analyses were performed. The intersected target list was uploaded to the web-based analytical tool which available at http://www.bioinformatics.com.cn/. The database consist of integratation of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses. GO terms were categorized into three domains: biological process (BP) , molecular function (MF) , and cellular component (CC) , providing insights into the functional roles of the targets. KEGG pathway analysis identified key signaling and metabolic pathways potentially modulated by *C. zedoaria* [23]. Statistical significance was determined using the Benjamini-Hochberg correction method, with a threshold of $p < 0.05$ considered significant [24]. This comprehensive enrichment analysis provided mechanistic insights into the molecular processes and pathways underlying the nephroprotective effects of *C. zedoaria* in CKD.

3. Result and discussion

3.1. Identification of bioactive compounds in C. zedoaria and their target profiles

A systematic search of Dr. Duke's Phytochemical and Ethnobotanical database identified a total of 19 naturally occurring bioactive compounds in *C. zedoaria*. To ensure relevance for pharmacological investigation and drug-like properties, these compounds were filtered based on adherence to the Lipinski Rule of 5, which predicts oral bioavailability and drug-likeness [25]. After

Table 1. Physicochemical properties and biological activity of natural compounds in *C. zedoaria*

Compounds	Activity count	Molecular weight	Log P	Rotatable bonds	H-bond acceptors	H-bond donors
Curcumin	135	368.385	3.3699	8	6	2
Eucalyptol	67	154.253	2.7441	0	1	0
Alpha-Pinene	28	136.238	2.9987	0	0	0
Dehydrocurdione	8	234.339	3.6174	0	2	0
Curdione	6	236.355	3.5532	1	2	0
Zingiberene	6	204.357	4.8913	4	0	0
Bisdemethoxycurcumin	5	308.333	3.3527	6	4	2
D-Borneol	4	154.253	2.1935	0	1	1
Curcumol	3	236.355	3.1123	1	2	1
Curcumenol	3	234.339	3.1765	0	2	1
Procurcumenol	2	234.339	3.0191	0	2	1
Epigoitrin	2	129.184	0.4457	1	2	1

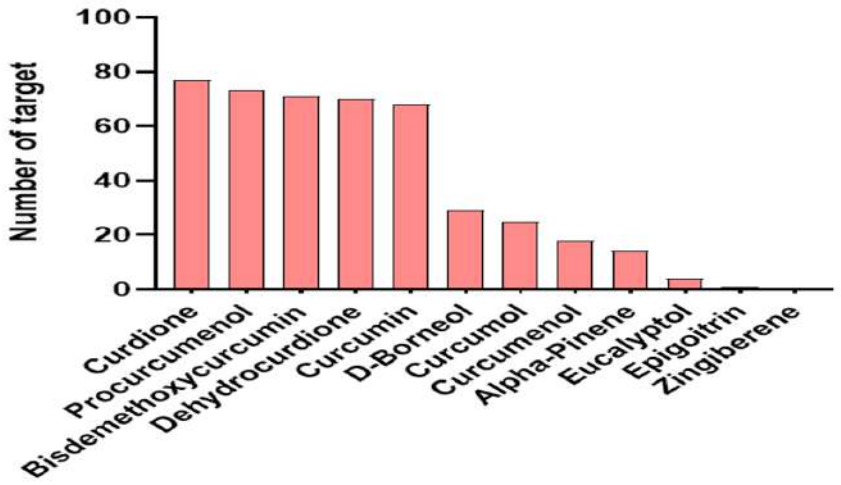

Figure 1. Number of predicted targets associated with major bioactive compounds of *C. zedoaria*

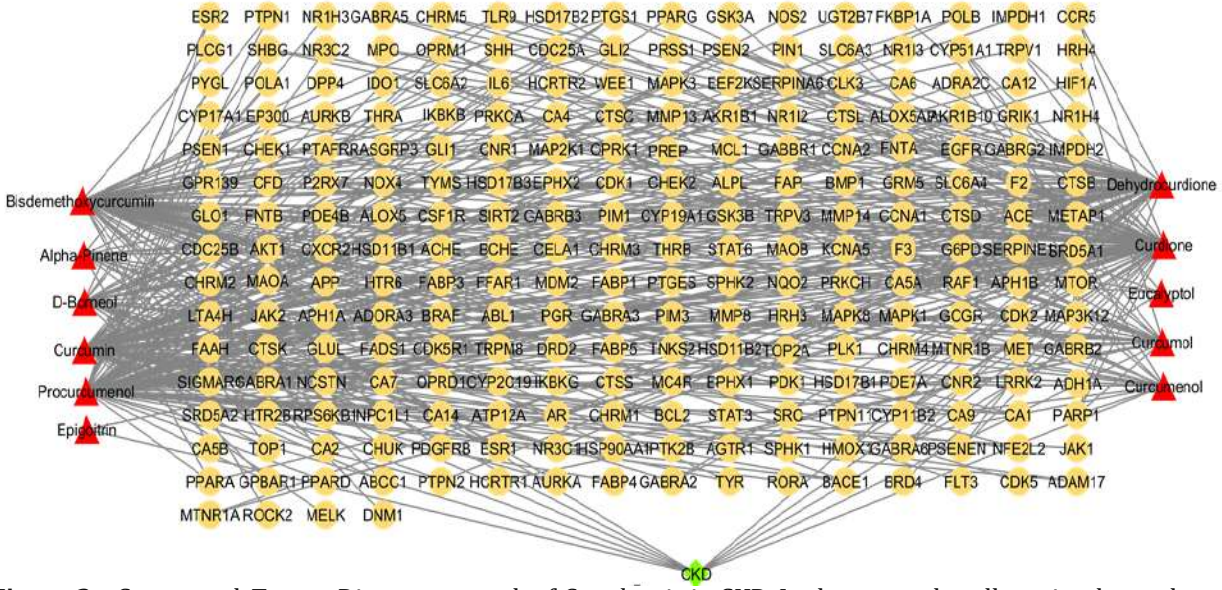

Figure 2. Compound–Target–Disease network of *C. zedoaria* in CKD. In the network, yellow circular nodes represent shared molecular targets of the compounds, red triangular nodes indicate bioactive compounds, the green diamond represents CKD, and the edges denote the interactions among these entities

applying this criterion, 12 compounds were retained for further analysis (Table 1). These compounds were selected based on their documented presence in *C. zedoaria*, evidence of biological activity, and compliance with pharmacokinetic parameters.

To assess the potential therapeutic relevance of these compounds, their predicted molecular targets were obtained using Swiss Target Prediction. Figure 1 illustrates the number of predicted targets for each compound. Among the bioactive compounds identified in *C. zedoaria*, curdione exhibited the highest number of predicted targets, with a total of 77. This was closely followed by procurcumenol (73 targets), bisdemethoxycurcumin (71 targets), and dehydrocurdione (70 targets), indicating their potential as multitarget agents. Curcumin showed interaction with 68 targets, suggesting significant biological activity. Other compounds such as D-borneol (29 targets) and curcumol (25 targets) also demonstrated moderate target interactions. Compounds like curcumenol (18 targets) and alpha-pinene (14 targets) had relatively fewer connections, while eucalyptol (4 targets) and epigoitrin (1 target) displayed limited target associations. Notably, zingiberene did not show any predicted targets, suggesting minimal molecular interaction within the context of this study. This variation in target profiles suggests that different compounds may exert their effects through distinct or overlapping mechanisms, contributing to the multitargeted nature of *C. zedoaria*.

To explore the multitarget mechanisms underlying the nephroprotective potential of *C. zedoaria*, an integrated compound–target–disease network was constructed using Cytoscape v3.10.3 and is presented in Figure 2. This network visualizes the complex interactions among selected bioactive compounds from *C. zedoaria*, their predicted molecular targets. The network reflects the polypharmacological nature of *C. zedoaria*, demonstrating how its active constituents may exert synergistic effects by modulating interconnected signaling pathways. This network provides a valuable framework for understanding the potential molecular basis of *C. zedoaria* for further experimental validation

3.2. Identification of CKD-associated targets

A comprehensive list of genes associated with CKD was generated by integrating differentially expressed genes from clinical datasets with curated disease-gene associations. Analysis of the GSE66494 dataset revealed significant gene expression changes between CKD patients and healthy controls. The top 100 differentially expressed genes (Figure 3), including 50 upregulated and 50 downregulated, were selected based on their expression magnitude and statistical significance. These gene expression findings were combined with data from the GeneCards database, which provided an extensive collection of CKD-related genes. After merging both datasets and eliminating duplicates, a final set of 13,878 unique CKD-associated targets was obtained. These targets represent key molecular players involved in various pathological processes linked to CKD, such as inflammation, oxidative stress, fibrosis, and immune dysfunction. The integration of experimental and literature-based data yielded a robust set of disease-relevant targets that reflect the complex molecular landscape of CKD. This expanded target list serves as a valuable resource for uncovering potential interactions with bioactive compounds from *C. zedoaria* and understanding their therapeutic relevance in renal disease.

3.3. Investigation of hub targets

To understand the potential molecular mechanisms by which *C. zedoaria* may exert therapeutic effects in CKD, a total of 241 intersecting targets were identified by overlapping the predicted targets of *C. zedoaria*-derived compounds with known CKD-related genes (Figure 4). These overlapping targets represented approximately 1.7% of the entire CKD-associated target database, suggesting a selective interaction with disease-relevant biological processes. The intersecting

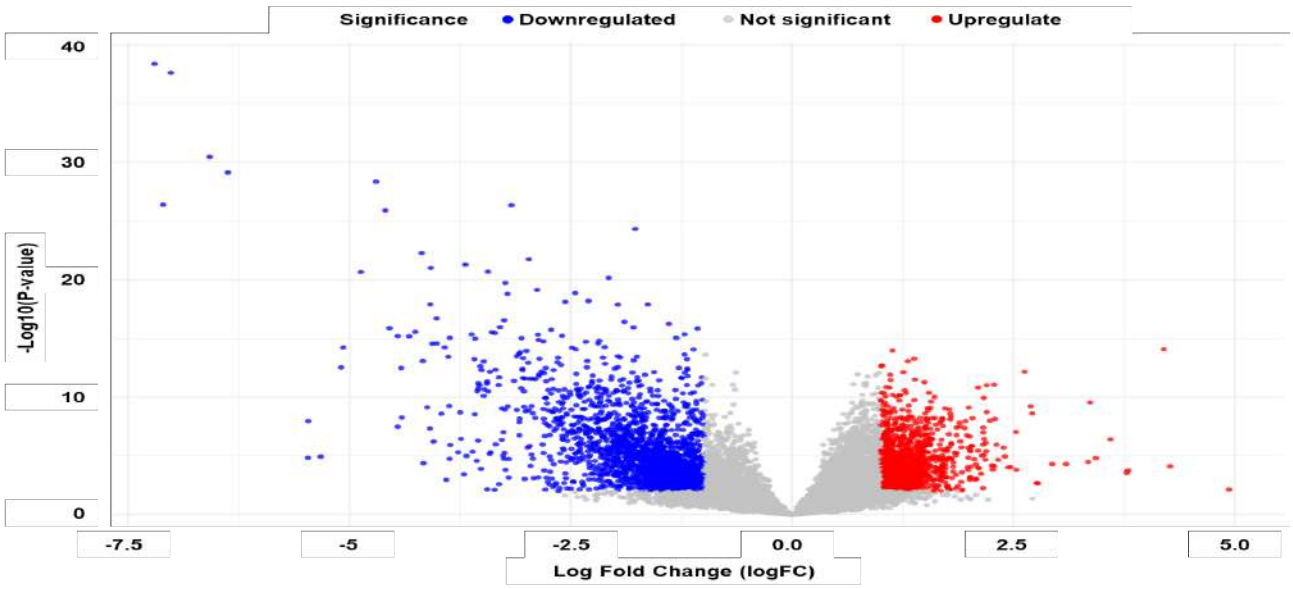

Figure 3. Volcano plot of differentially expressed genes in CKD dataset. Red dots represent significantly upregulated genes, while blue dots indicate significantly downregulated genes. Gray dots denote genes with no significant change

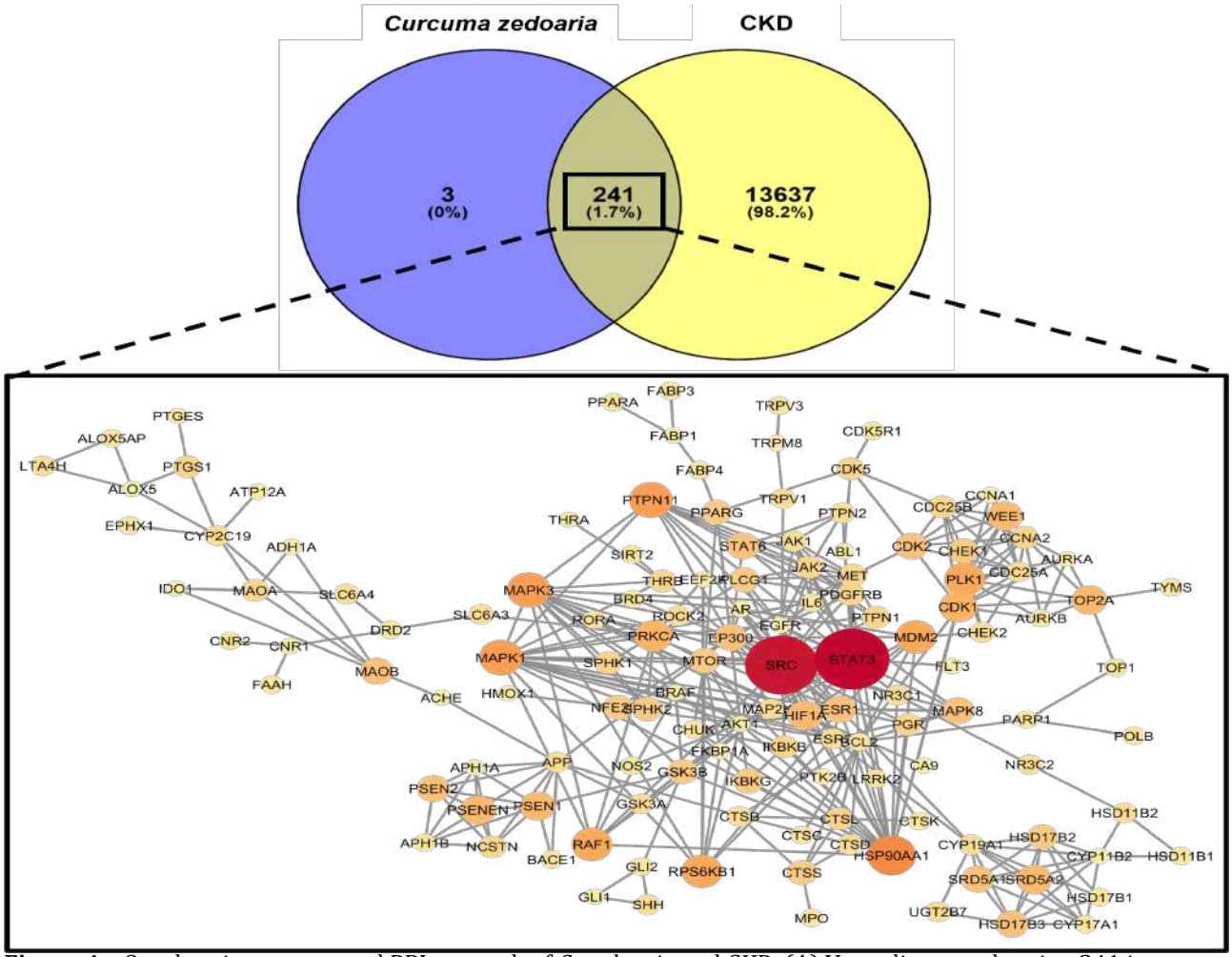

Figure 4. Overlapping targets and PPI network of *C. zedoaria* and CKD. (A) Venn diagram showing 241 intersecting targets between *C. zedoaria* -associated compounds and CKD-related genes, accounting for 1.7% of the total CKD gene dataset. (B) PPI network of the intersecting targets constructed using STRING and visualized in Cytoscape. Node size and color intensity both correspond to degree, with larger and darker nodes indicating proteins with more interactions

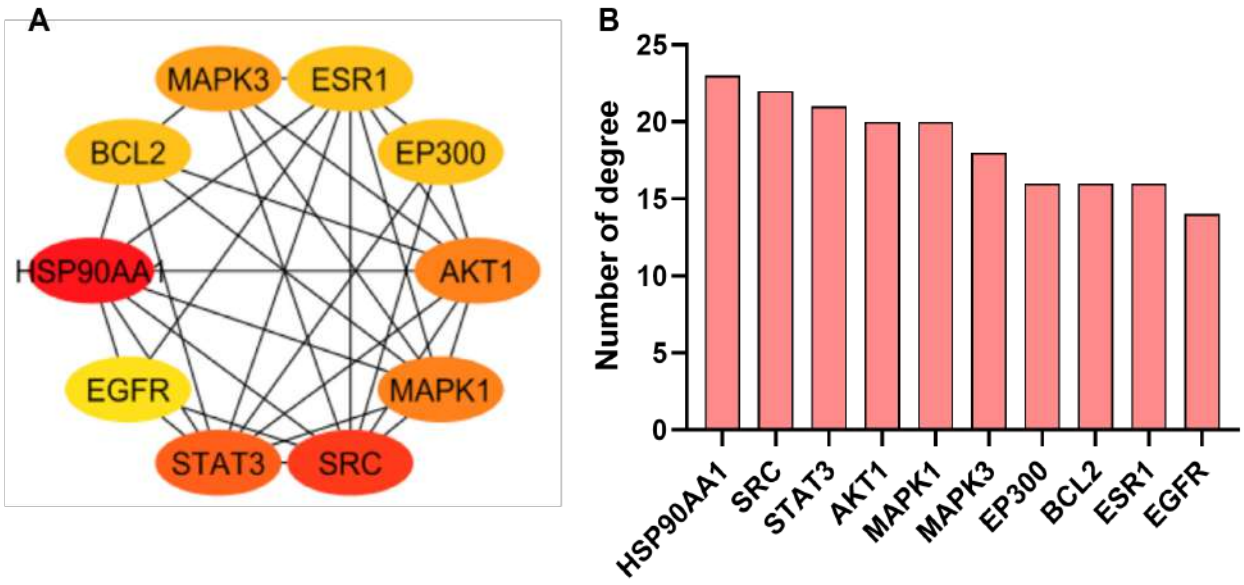

Figure 5. Identification of top 10 hub targets based on degree in the PPI Network. (A) Network layout of the top 10 hub proteins, where node color intensity reflects degree, with darker nodes indicating higher connectivity. (B) Bar graph ranking the hub proteins by degree value, showing HSP90AA1, SRC, and STAT3 as the most connected targets, suggesting their critical regulatory roles in the CKD-related network

targets were used to generate a protein–protein interaction (PPI) network, and topological analysis revealed several highly interconnected hub nodes. As shown in Figure 5, the top ten hub targets were identified based on their degree values, indicating their potential central roles in the therapeutic mechanism of *C. zedoaria* against CKD. From this analysis, ten key proteins were highlighted as hub targets (Figure 5A), including Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1; degree = 23), SRC Proto-Oncogene, Non-Receptor Tyrosine Kinase (SRC; degree = 22), Signal Transducer and Activator of Transcription 3 (STAT3; degree = 21), AKT Serine/Threonine Kinase 1 (AKT1; degree = 20), Mitogen-Activated Protein Kinase 1 (MAPK1; degree = 20), Mitogen-Activated Protein Kinase 3 (MAPK3; degree = 18), E1A Binding Protein P300 (EP300; degree = 16), BCL2 Apoptosis Regulator (BCL2; degree = 16), Estrogen Receptor 1 (ESR1; degree = 16), and Epidermal Growth Factor Receptor (EGFR; degree = 14) (Figure 5B). These hub nodes represent central regulators within the network and are likely to have significant roles in mediating the pharmacological effects of *C. zedoaria* in CKD.

HSP90AA1 encodes a chaperone protein that maintains the stability and function of various signaling proteins. It has been implicated in oxidative stress responses and may regulate the stability of fibrosis-related factors in CKD [26]. STAT3, a key transcription factor, is known to mediate inflammatory and fibrotic gene expression. Its aberrant activation contributes to renal scarring and chronic inflammation, both hallmarks of CKD progression [27]. SRC is a tyrosine kinase that plays a role in transducing signals for cell adhesion, proliferation, and fibrotic responses; its dysregulation can lead to tissue remodeling in diseased kidneys [28]. AKT1 functions in the PI3K/AKT pathway, promoting cell survival and metabolic regulation. Overactivation of AKT1 has been associated with impaired autophagy and tubular injury in CKD [29]. The mitogen-activated protein kinases MAPK1 (ERK2) and MAPK3 (ERK1) are involved in cellular responses to stress, inflammation, and growth factors [30]. Persistent MAPK signaling can exacerbate renal fibrosis and hypertrophy [31]. EGFR regulates epithelial regeneration and survival but, when overactivated, may promote fibrotic changes and glomerular injury [32]. ESR1, or estrogen recep-

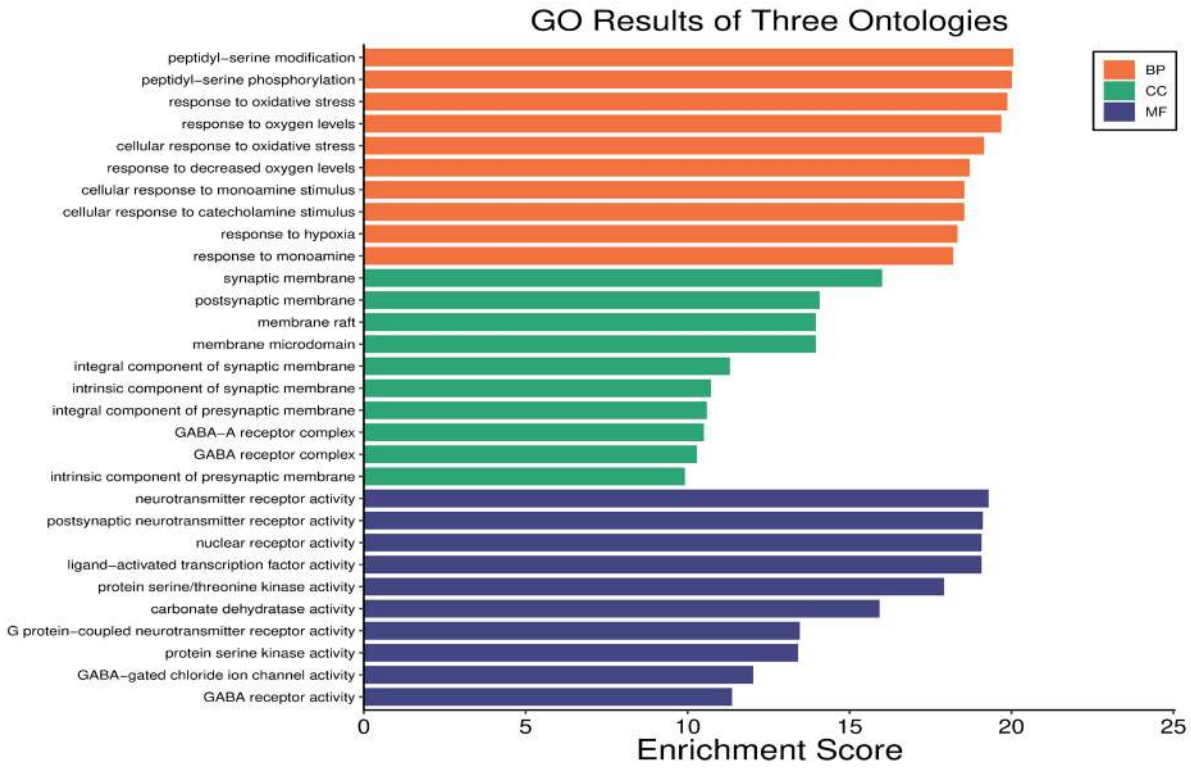

Figure 6. GO enrichment analysis of overlapping targets. Bar plot showing the top enriched terms from three GO categories: biological process (BP, orange), cellular component (CC, green), and molecular function (MF, blue)

tor alpha, influences renal physiology through hormonal modulation, with evidence suggesting its protective effects against oxidative damage and inflammation in renal tissue [33]. BCL2 is an anti-apoptotic protein that prevents programmed cell death. While beneficial in preventing tubular cell loss, excessive BCL2 activity may hinder the clearance of damaged cells, thereby contributing to fibrosis [34]. Lastly, EP300 encodes a histone acetyltransferase that serves as a transcriptional co-activator and plays a role in chromatin remodeling. EP300 has been linked to the regulation of fibrotic and inflammatory gene expression, suggesting its involvement in long-term epigenetic alterations during CKD development [35].

In summary, these ten hub proteins are closely linked to the key biological processes underlying CKD, including inflammation, oxidative stress, apoptosis regulation, and fibrogenesis. Their centrality in the PPI network underscores their potential as therapeutic targets modulated by active compounds in *C. zedoaria*. These targets will be further explored through pathway enrichment and molecular docking analyses to validate their relevance in *C. zedoaria*-based interventions for CKD.

3.4. GO and KEGG-based functional annotation of core targets

To further elucidate the biological functions and signaling pathways associated with the top hub targets, enrichment analyses were performed using GO and KEGG databases. These analyses provided comprehensive insight into the biological processes (BP), cellular components (CC), molecular functions (MF), and key signaling pathways potentially regulated by *C. zedoaria*-associated targets in the context of CKD. The GO enrichment analysis revealed that the candidate targets were primarily involved in several critical biological processes, including peptidyl-serine modification, response to oxidative stress, response to monoamine stimulus, and response to hypoxia (Figure 6). These processes are highly relevant to CKD pathology, as oxidative stress and hypoxic injury are central contributors

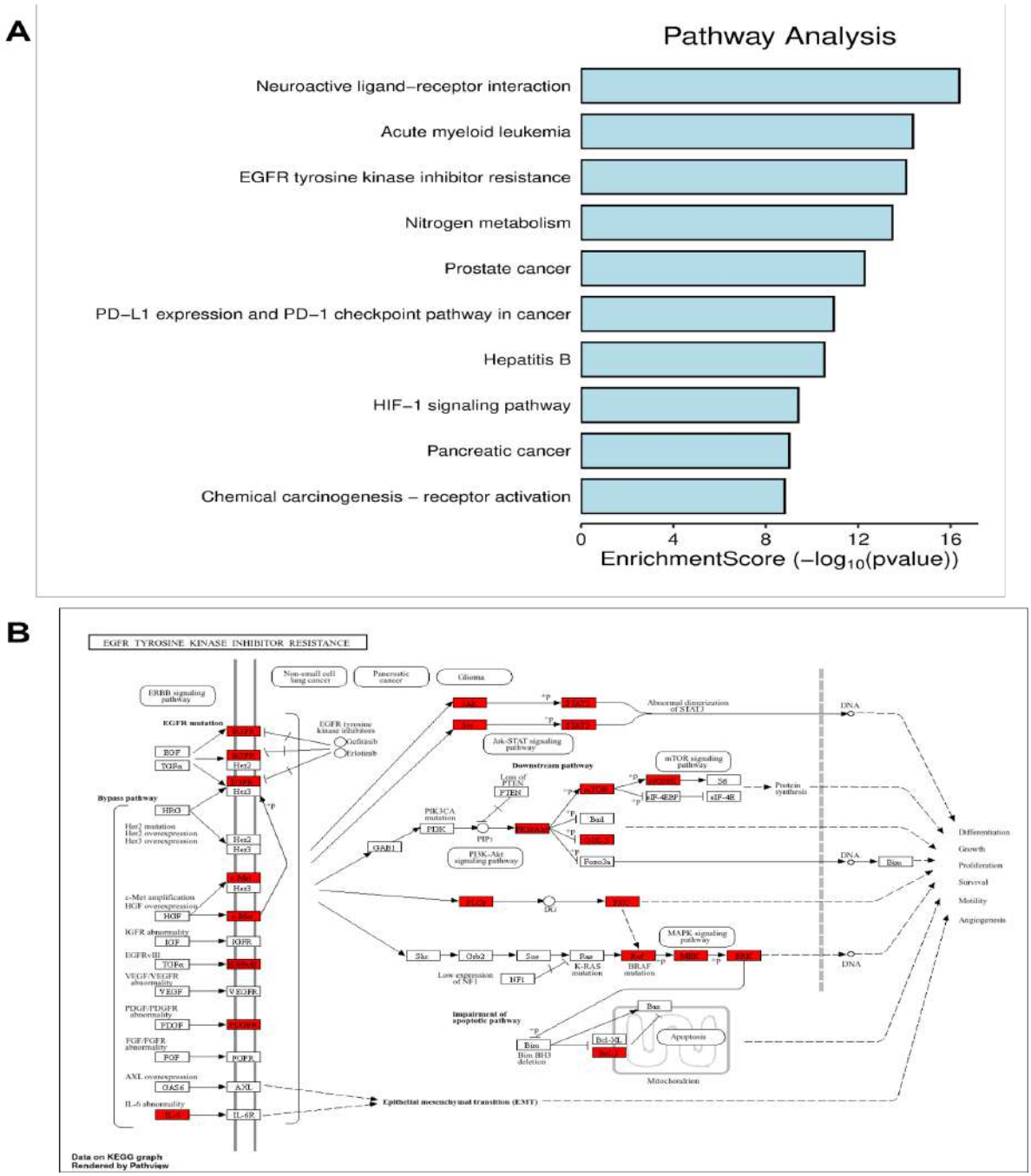

Figure 7. KEGG pathway enrichment and mapping of hub targets. (A) Bubble plot of the top enriched KEGG pathways associated with overlapping targets. Bubble size reflects the number of involved genes, and color intensity indicates statistical significance (p-value). (B) Detailed KEGG pathway map of the EGFR tyrosine kinase inhibitor resistance pathway. Highlighted red nodes represent hub targets mapped within the pathway, including STAT3, AKT1, SRC, MAPK1, MAPK3, BCL2, and EP300, suggesting their functional relevance in CKD-related signaling and therapeutic modulation by *C. zedoaria*

to renal inflammation, fibrosis, and progressive nephron loss. From the cellular component category, enriched terms included synaptic membrane, postsynaptic membrane, membrane raft, and GABA receptor complex, suggesting possible interactions with membrane-bound receptors or ion channels in renal tissue. In the molecular function category, significant terms such as neurotransmitter receptor activity, nuclear receptor activity, ligand-activated transcription factor activity, and protein kinase activity were identified. These findings suggest that the core targets may

function through transcriptional regulation and intracellular signal transduction, particularly in response to stress stimuli and hormonal cues.

In addition to GO terms, KEGG pathway analysis was conducted to explore specific disease-related and regulatory pathways (Figure 7A). Among the most significantly enriched pathways were neuroactive ligand–receptor interaction, acute myeloid leukemia, EGFR tyrosine kinase inhibitor resistance, and the HIF-1 signaling pathway. Notably, the EGFR tyrosine kinase inhibitor resistance pathway (Figure 7B) showed substantial involvement of the hub targets, including STAT3, AKT1, SRC, MAPK1, MAPK3, BCL2, and EP300. This pathway is of particular interest in CKD, as it intersects with inflammation, apoptosis resistance, cellular proliferation, and epithelial-to-mesenchymal transition (EMT) mechanisms known to drive renal fibrosis and disease progression [36,37]. The enrichment of HIF-1 signaling further supports the involvement of hypoxia-driven gene expression changes in CKD pathogenesis [38,39]. The identification of cancer-related pathways such as PD-L1 checkpoint regulation also reflects the shared molecular features between renal injury and tumor-like tissue remodeling processes, including chronic inflammation and resistance to cell death [40].

Taken together, the GO and KEGG analyses highlight a complex network of biological functions and signaling cascades regulated by *C. zedoaria*-derived targets. These targets appear to act through modulation of oxidative stress responses, hypoxia adaptation, inflammatory signaling, and transcriptional regulation, supporting their potential utility in the development of multi-target therapies for CKD.

4. Conclusion

This study employed a network pharmacology approach to explore the nephroprotective potential of *C. zedoaria* in CKD. Through systematic target prediction and integration with CKD-associated genes, 241 shared targets were identified. Network analysis highlighted key compounds such as curdione and dehydrocurdione, which interact with central hub proteins including STAT3, MAPK3, AKT1, and HSP90AA1 that involved in inflammation, oxidative stress, and fibrosis. Functional enrichment revealed significant involvement of pathways such as EGFR tyrosine kinase inhibitor resistance and HIF-1 signaling, suggesting that *C. zedoaria* exerts its effects through multitarget modulation of CKD-related mechanisms. These findings provide a theoretical basis for further experimental studies on the therapeutic application of *C. zedoaria* in renal diseases.

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