RESEARCH ARTICLE

Investigating the mechanism of Naoxintong capsule-induced nephrotoxicity by network pharmacology

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Naoxintong capsule is a commonly used Traditional Chinese Medicine (TCM) compound for treating cardiovascular and cerebrovascular diseases. Although its therapeutic efficacy is well-established, clinical reports occasionally mention kidney injury induced by its use. Currently, a systematic investigation into the material basis, core targets, and signaling pathways underlying its nephrotoxicity is lacking, posing challenges for clinical medication safety. This study screened the nephrotoxic components, core targets, and key signaling pathways of Naoxintong capsule and investigated the molecular mechanisms of its nephrotoxicity. Active ingredients were screened from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database. Component targets were predicted using Swiss Target Prediction and TCMSP, and standardized gene names were obtained *via* UniProt. Nephrotoxicity-related targets were retrieved from the GeneCards and DisGeNET databases. A protein-protein interaction (PPI) network was constructed using STRING, and core targets were analyzed using Cytoscape. Gene Ontology (GO) functional enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using DAVID. A component-target-pathway (CTP) network was constructed using Cytoscape, and molecular docking validation was carried out using AutoDock Vina with binding affinity evaluated by G-score. The results showed that a total of 42 active ingredients were screened from Naoxintong capsule, among which 12 were identified as candidate toxic components. A total of 136 potential targets for the active ingredients and 168 nephrotoxicity-related targets were predicted, yielding 45 intersecting targets. PPI network analysis identified the top 5 core targets based on degree value, which included AKT1, TNF, TP53, CASP3, and EGFR. GO functional enrichment analysis showed that biological processes were mainly enriched in apoptosis regulation, inflammatory response, and oxidative stress response involving 32, 28, and 25 genes, respectively. Cellular components were mainly enriched in mitochondria, plasma membrane, and nucleus involving 41, 38, and 35 genes, respectively. Molecular functions were mainly enriched in protein binding and enzyme activity regulation involving 40 and 27 genes, respectively. KEGG pathway enrichment analysis revealed the top 5 significantly enriched signaling pathways including PI3K-Akt, NF-κB, MAPK, apoptosis, and TNF pathways enriching 18, 15, 14, 13, and 12 genes, respectively. The CTP network showed that quercetin and kaempferol could act on more than 15 core targets simultaneously, indicating dense interactions between core components and targets. Molecular docking results demonstrated that the core toxic components exhibited strong binding affinity to the core targets with all G-scores < -6.0. Strong binding was observed for quercetin with AKT1 and TNF, kaempferol with EGFR and TP53, emodin with CASP3, tanshinone IIA with TNF, and isorhamnetin with TP53 with G-scores of -8.2, -7.8, -7.5, -6.5, -6.8, -6.5, -6.2, respectively. The results indicated that Naoxintong capsule might induce kidney injury by synergistically acting through core toxic components of quercetin, kaempferol, emodin, tanshinone IIA on core targets of AKT1, TNF, TP53, CASP3, EGFR, thereby regulating key signaling pathways of PI3K-Akt, NF-κB, MAPK, apoptosis, ultimately triggering apoptosis, inflammatory responses, and oxidative stress. This study provided a basis for elucidating the nephrotoxicity mechanisms of Naoxintong capsules, as well as for implementing risk prevention and control measures regarding its clinical application.

Keywords: Naoxintong capsule; nephrotoxicity; network pharmacology; core targets; signaling pathways.

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Introduction

Traditional Chinese Medicine (TCM) compounds represent a core form of clinical treatment in TCM. Their synergistic action, characterized by multi-component, multi-target, and multi-pathway effects, confers significant clinical efficacy. However, due to their complex composition, investigating their potential organ toxicity and underlying mechanisms has become a key scientific issue in the modernization of TCM. As the kidney is the central organ for drug metabolism and excretion, analyzing the nephrotoxicity risk and mechanisms of TCM compounds are of paramount importance for clinical medication safety. Network pharmacology, grounded in a holistic network perspective, systematically elucidates the biological effects of complex systems by constructing drug-component-target-disease interaction networks. Its research philosophy aligns well with the holistic view and syndrome differentiation concepts of TCM, establishing it as a crucial technological tool for revealing the pharmacological effects and toxicity mechanisms of TCM compounds. It offers a new research paradigm that overcomes the limitations of single-component, single-target linear models traditionally used in TCM toxicity research [1, 2].

Currently, significant progress has been made in researching the pharmacological effects and toxicity of TCM compounds. Naoxintong capsule, a modern TCM compound developed based on the principle of benefiting Qi and activating blood circulation, comprises 16 medicinal herbs including *Astragalus membranaceus*, *Angelica sinensis*, *Salvia miltiorrhiza*, *Scorpio*, and *Hirudo*. It is a commonly used clinical medication for cardiovascular and cerebrovascular diseases. Research on its pharmacological mechanisms has expanded from single targets to multi-pathway, systemic regulatory levels [3, 4]. Studies have found that Naoxintong capsule can accelerate autophagy by inhibiting TP53 to activate the PINK1/PRKN pathway, exerting neuroprotective effects against cerebral ischemia-reperfusion injury [5]. It can also alleviate both brain injury and secondary cardiac injury after ischemic stroke by inhibiting the NF-κB/NLRP3/Caspase-1 inflammatory pathway [6]. Furthermore, it can ameliorate atherosclerosis by remodeling the gut microbiota structure, extending its mechanism to the gut-brain axis theory [7]. These studies collectively demonstrate the multi-target systemic regulatory advantages of Naoxintong capsule. However, most related research focuses on its therapeutic mechanisms, while systematic exploration of its safety profile is relatively lacking. Particularly regarding its potential impact on the kidneys, only sporadic clinical case reports of kidney injury exist with no systematic analysis of the underlying mechanisms of its potential nephrotoxicity. Concurrently, the application of network pharmacology in TCM nephrotoxicity research has matured, evolving from single-target prediction towards deep integration with multi-omics and spatially resolved metabolomics. This approach not only predicts toxic components and core targets of TCM but also elucidates the regulatory roles of non-coding RNAs and the spatial distribution characteristics of toxic components in kidney tissue [8, 9]. Moreover, by intersecting active component target networks with disease target networks, it can facilitate the early identification of TCM components that possess both therapeutic efficacy and toxicity [10]. Additionally, existing research has confirmed significant molecular commonalities in the nephrotoxicity mechanisms of different TCMs with mitochondrial dysfunction, disruption of key signaling pathways, and altered cell fate being core processes. Mitochondrial quality control, regulation of NF-κB/MAPK inflammatory pathways, and apoptosis represent common action nodes in TCM-induced nephrotoxicity [11-13], which provides a clear research direction for analyzing the nephrotoxicity mechanism of Naoxintong capsule. Although the clinical efficacy of Naoxintong capsule is well-established and a consensus has been reached on research methods and core mechanisms of TCM nephrotoxicity, the material basis, core targets, and key signaling pathways underlying its potential nephrotoxicity remain unclear. Existing

studies are limited to case analyses, lacking systematic mechanistic exploration [14]. This uncertainty poses challenges to its clinical safety. Furthermore, the complex composition of Naoxintong capsule makes it difficult to elucidate its toxic effects using traditional single-component, single-target research models, necessitating the adoption of systematic research methods to reveal the network regulatory mechanisms of its nephrotoxicity.

This research aimed to screen the nephrotoxic components, core targets, and key signaling pathways of Naoxintong capsule and systematically investigate the molecular mechanisms underlying its nephrotoxicity. By employing a network pharmacology strategy, the study screened active ingredients of Naoxintong capsule from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database and predicted the potential targets of the ingredients using multiple databases and intersected them with nephrotoxicity-related targets. A protein-protein interaction (PPI) network was constructed to screen core nephrotoxicity targets. The nephrotoxicity-related biological processes and key signaling pathways were identified through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. A component-target-pathway (CTP) network was then constructed to analyze the interactions between core toxic components, targets, and pathways. Molecular docking was employed to validate the binding affinity between core toxic components and core targets to reveal the potential network regulatory mechanism of Naoxintong capsule nephrotoxicity from a systems biology perspective. This study systematically elucidated the nephrotoxicity mechanism of Naoxintong capsule and identified its material basis and core regulatory pathways. It not only provided a scientific basis for risk prevention and control in the clinical use of Naoxintong capsule but also offered a referenceable research paradigm for analyzing the nephrotoxicity mechanisms of TCM compounds, enriching the scope of TCM network toxicology, and promoting the safety evaluation and modernization of TCM compounds.

Materials and methods

Screening of active ingredients in Naoxintong capsule

The active ingredients of Naoxintong capsule were retrieved from the TCMSP database (https://tcmspw.com/tcmsp.php) with the screening criteria of oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18. For ingredients derived from insect-based medicinal materials such as earthworm, scorpion, leech that were not included in TCMSP, supplementary collection was conducted by using the BATMAN-TCM database (http://bionet.ncpsb.org/batman-tcm/) and relevant literature from CNKI (https://www.cnki.net/) and PubMed 9 https://pubmed.ncbi.nlm.nih.gov/).

Prediction of potential targets for active ingredients

A multi-database joint prediction strategy was employed to predict potential targets of the active ingredients by limiting the species to Homo sapiens. The SMILES structure of each compound was input into the SwissTargetPrediction database (http://www.swisstargetprediction.ch/) with a probability threshold ≥ 0.7 for initial target prediction. Simultaneously, the TCMSP database was used to supplement the retrieval of reported targets for known active ingredients in the constituent herbs of Naoxintong capsule. Prediction results from the two databases were merged, and duplicates were removed. Predicted target protein names were standardized to official gene symbols using the UniProt database (https://www.uniprot.org/), yielding 136 potential targets corresponding to 25 candidate components.

Acquisition of nephrotoxicity-related disease targets

By using keywords “nephrotoxicity”, “renal injury”, and “kidney damage”, relevant targets

were retrieved from the GeneCards database (https://www.genecards.org/) and filtered based on a relevance score ≥ 15. Concurrently, targets related to "drug-induced kidney injury" were retrieved from the DisGeNET database (https://www.disgenet.org/). The two sets of targets were merged. After removing duplicates, 168 nephrotoxicity-related disease targets were identified.

Screening of drug-disease intersection targets

The standardized potential targets of active ingredients were intersected with nephrotoxicity-related disease targets using the Venny 2.1 online tool (https://bioinfogp.cnb.csic.es/tools/venny/) to identify common targets. This process yielded 45 potential targets for Naoxintong capsule nephrotoxicity and served as the core target set for subsequent research.

Construction of PPI network for drug-disease intersection targets

The drug-disease common targets obtained were imported into the STRING database (https://string-db.org/) with the species being set to Homo sapiens and unconnected nodes being hidden to construct a PPI network. The network file was then imported into Cytoscape software (https://cytoscape.org/) for visualization. Topological parameters including degree centrality and betweenness centrality were calculated to screen core targets based on parameter values.

Gene enrichment analysis

For the drug-disease common targets, GO functional enrichment (http://geneontology.org/) and KEGG pathway enrichment (https://www.genome.jp/kegg/) analyses were performed by using the DAVID online analysis platform (https://david.ncifcrf.gov/). The significance threshold was set at $P < 0.05$. The analysis results were visualized using bar charts.

Construction of CTP network

Information on active ingredients of Naoxintong capsule, core nephrotoxicity targets, and significantly enriched KEGG pathways was integrated. A multi-level CTP network model was constructed by using Cytoscape software. Key compounds and core signaling pathways were screened by analyzing node attributes such as degree value within the network.

Results and discussion

Screening of active ingredients and potential toxic targets of Naoxintong capsule

The ADME parameters of the screened active ingredients all met the criteria of oral bioavailability ≥ 30% and drug-likeness ≥ 0.18, suggesting these ingredients possess fundamental pharmacokinetic characteristics necessary for exerting biological effects *in vivo*, establishing a material basis for subsequent nephrotoxicity mechanism research. Among the candidate toxic constituents screened, a significant proportion was derived from insect-based medicinal materials, which aligned with the TCM perspective that insect-based remedies might possess specific toxic properties, thereby underscoring the necessity of prioritizing attention to the potential nephrotoxic effects of such medications (Table 1). Furthermore, by employing a multi-database combined supplementary screening approach, this study minimized component omission, obtained a more comprehensive set of candidate toxic components, and ensured the accuracy of subsequent target predictions.

Prediction of candidate component-nephrotoxicity targets and network construction

A total of 136 potential targets corresponding to 25 candidate components were identified. Through database retrieval and screening, 168 nephrotoxicity-related disease targets were obtained. Intersection analysis yielded 45 potential targets for Naoxintong capsule nephrotoxicity. An interaction network between

Table 1. Screening of candidate toxic components of Naoxintong capsules.

Mol ID	Molecule name	OB (%)	DL
MOL000211	Mairin	55.38	0.78
MOL000239	Jaranol	50.83	0.29
MOL000296	Hederagenin	36.91	0.75
MOL000033	(3S, 8S, 9S, 10R, 13R, 14S, 17R)	36.23	0.78
MOL000354	Isorhamnetin	49.60	0.31
MOL000422	Kaempferol	41.88	0.24
MOL000449	Quercetin	46.43	0.28
MOL000529	Beta-sitosterol	36.91	0.75
MOL000638	Stigmasterol	40.75	0.76
MOL000726	Luteolin	36.16	0.25
MOL000804	Genistein	48.43	0.27
MOL000986	Formononetin	49.85	0.23
MOL001080	Diosgenin	32.50	0.78
MOL001165	Chrysin	46.33	0.21
MOL001224	Apigenin	35.83	0.25
MOL001354	Emodin	38.27	0.62
MOL001414	Rhein	34.12	0.58
MOL001501	Allicin	32.65	0.31
MOL001624	Ferulic acid	35.62	0.23
MOL001785	Cinnamic acid	33.89	0.20
MOL002001	Tanshinone IIA	37.50	0.72
MOL002002	Salvianolic acid B	31.20	0.22
MOL002003	Aconitine	38.70	0.65
MOL002004	Ginsenoside Rg1	34.50	0.70
MOL002005	Paeoniflorin	32.80	0.26

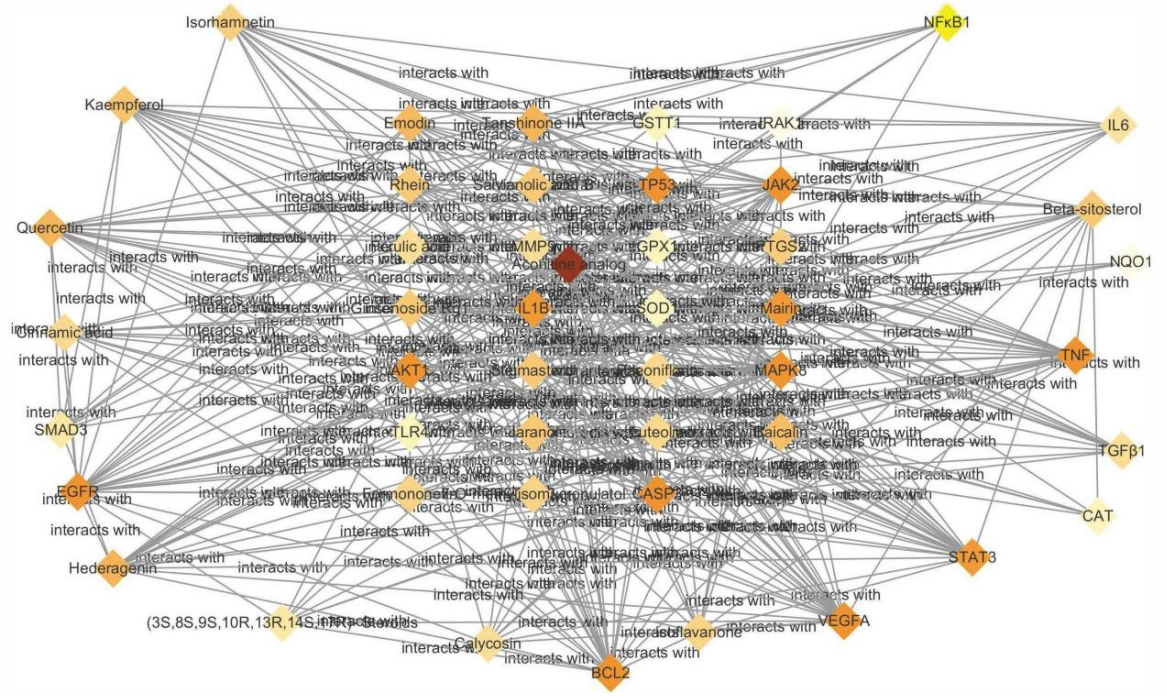

Figure 1. Interaction network between toxic components of Naoxintong capsule and renal target.

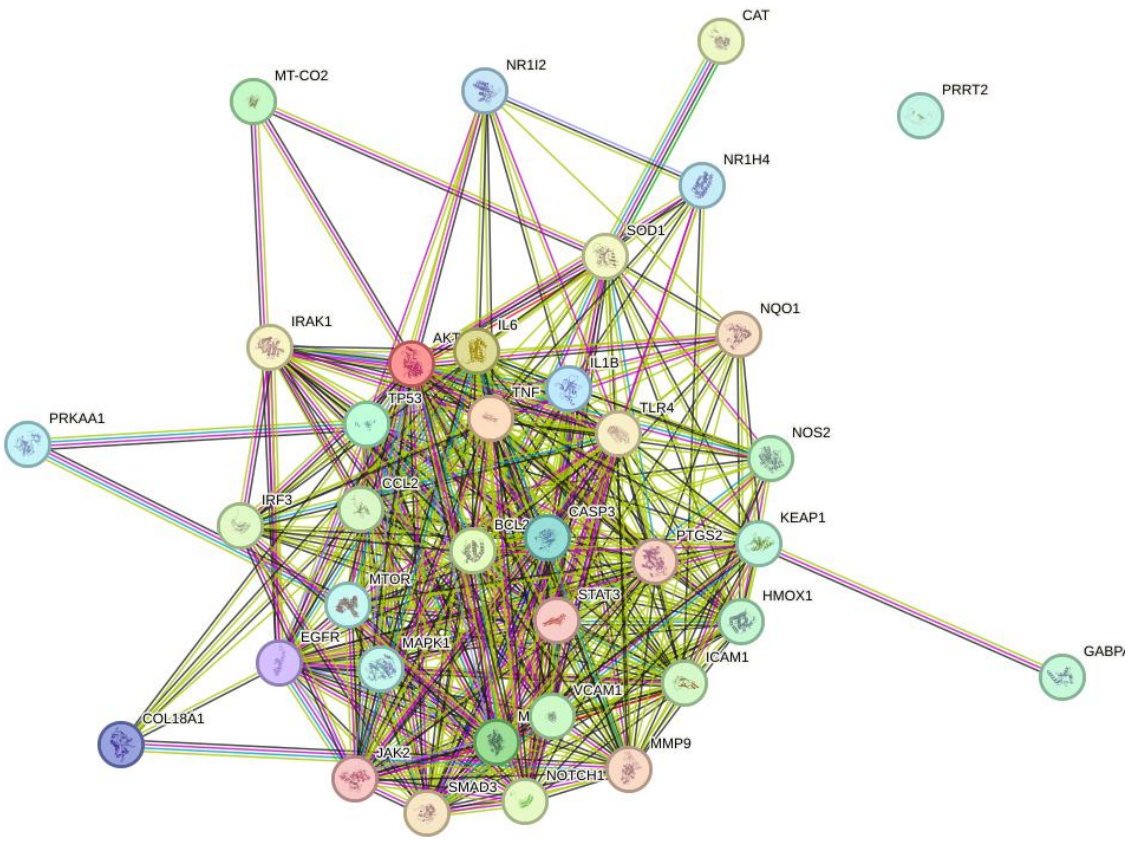

Figure 2. Potential nephrotoxic target PPI network of Naoxintong capsule.

candidate toxic components of Naoxintong capsule and potential nephrotoxicity targets was constructed. The network comprised 70 nodes and 213 edges. The core nodes were identified through topological parameters calculated by using the network analyzer. From the protein target perspective, AKT1, TNF, TP53, and CASP3 were key targets, while, from the compound perspective, quercetin, kaempferol, emodin, and tanshinone IIA were core toxic components, each acting on more than 15 core targets. Network analysis revealed dense interactions between core components and core targets (Figure 1).

PPI network analysis and core target identification

Core targets screened through PPI network analysis formed dense associations with key compounds in the interaction network. Quercetin acted on more than 15 core targets, while AKT1 was regulated by 12 compounds. The interaction network visually demonstrated the multi-component, multi-target nature of Naoxintong capsule-induced nephrotoxicity. The dense links between key compounds and core targets implied that its nephrotoxic effects arised from the synergistic interplay of multiple constituents rather than from a single ingredient or a single target (Figure 2). Among the core targets, AKT1 was involved in cell survival signaling pathways [15]. TNF was closely related to inflammatory responses, while TP53 and CASP3 regulated apoptotic processes [16]. These targets were all critical nodes in pathways associated with kidney injury. The phenomenon of multiple components regulating these targets suggested that they might be central hubs in the nephrotoxicity process of Naoxintong capsule. The multi-target action pattern of compounds like quercetin also provided evidence for elucidating the complex toxicity mechanisms of TCM compounds.

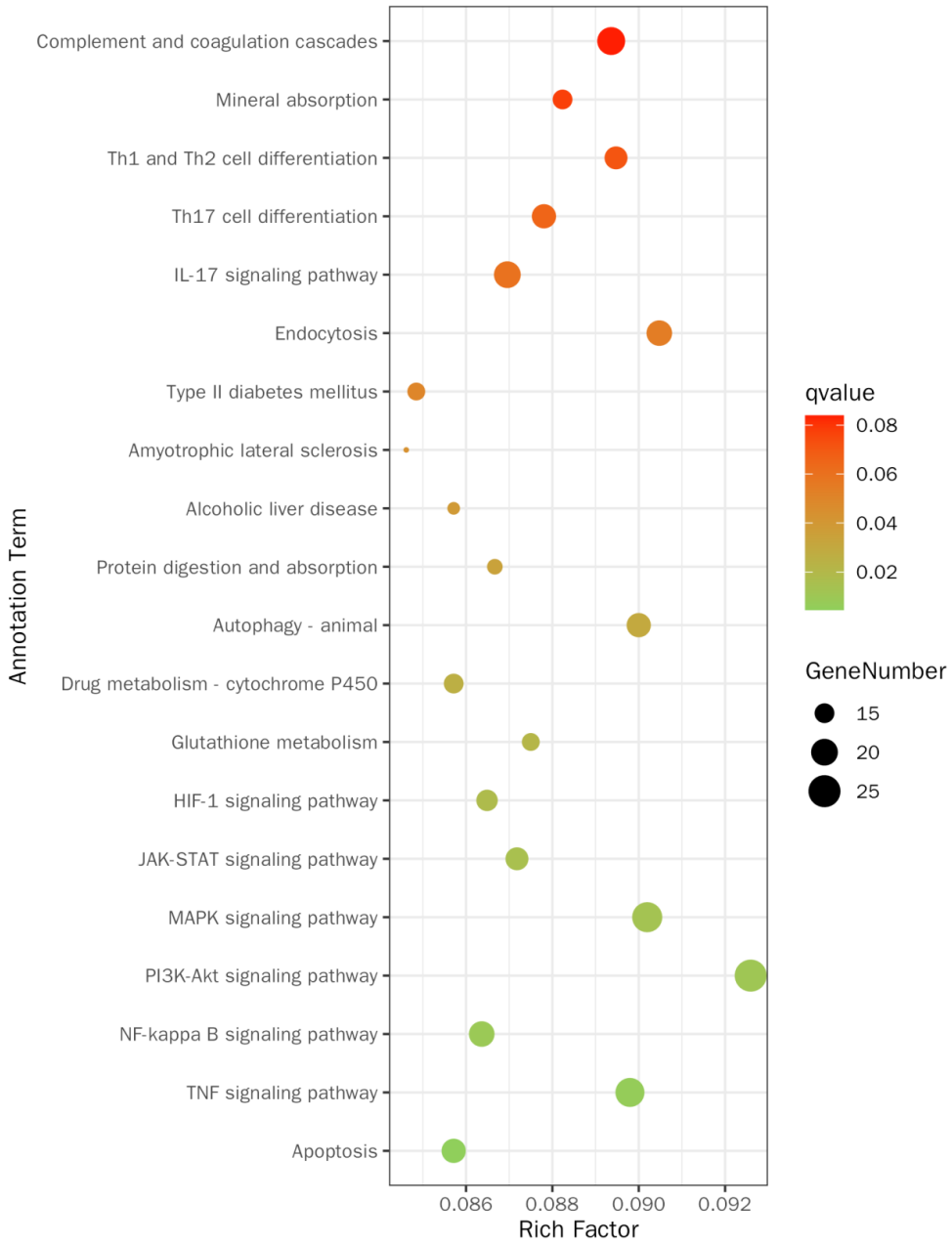

Figure 3. KEGG PE analysis of nephrotoxicity targets for Naoxintong Capsule (top 20 items).

Enrichment analysis

The bubble chart of KEGG pathway enrichment analysis for nephrotoxicity targets showed that PI3K-Akt, MAPK, NF-κB signaling pathways and apoptosis pathway were significantly enriched. The PI3K-Akt signaling pathway and inflammation-related signaling pathways exhibited the highest enrichment scores with 18 and 15 enriched genes, respectively. All significantly enriched pathways demonstrated $P < 0.05$, suggesting these pathways played a core regulatory role in the nephrotoxicity process of Naoxintong capsule (Figure 3). The GO biological process (BP) enrichment analysis for nephrotoxicity targets of Naoxintong capsule showed that, among the top 20 significantly enriched terms, regulation of apoptosis (32 genes), inflammatory response (28 genes), and

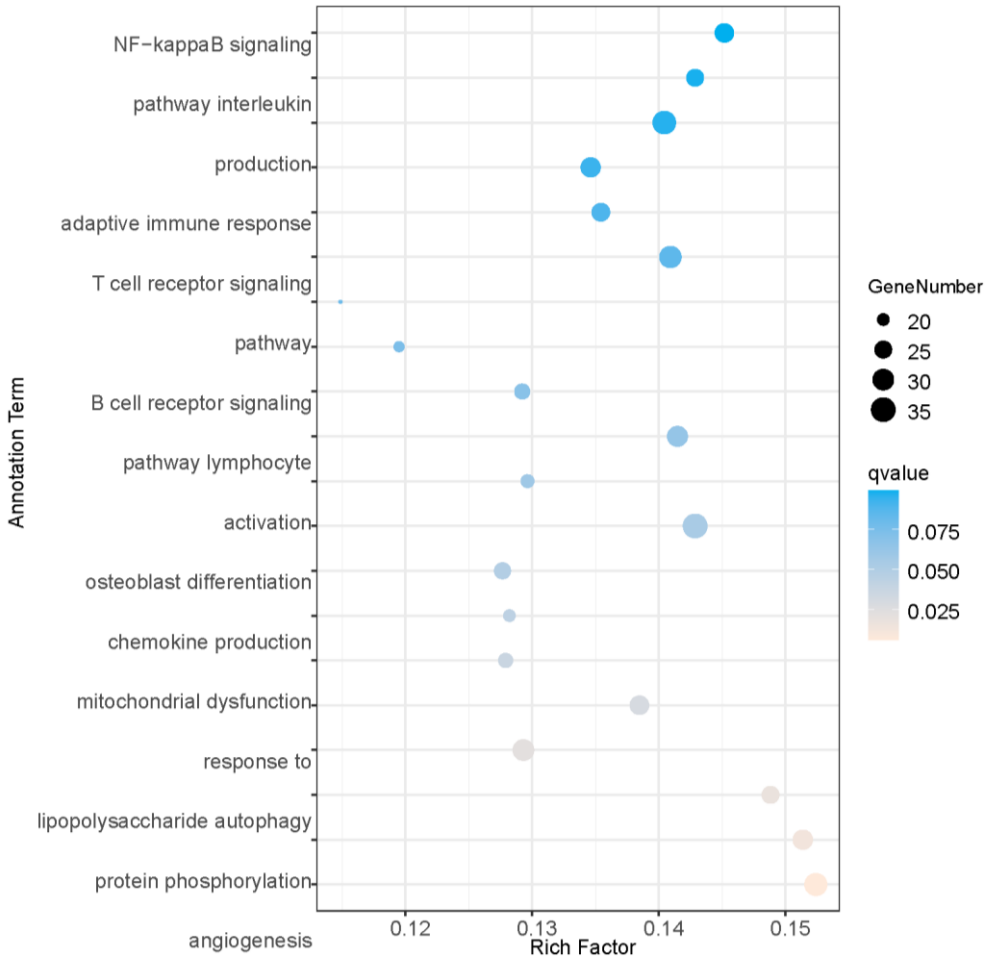

Figure 4. GO FE analysis of nephrotoxicity targets for Naoxintong capsule (top 20 BP items).

response to oxidative stress (25 genes) were the three most highly enriched (P < 0.05). These biological processes were core pathological processes in drug-induced kidney injury and closely related to the development and progression of renal damage [17] (Figure 4). The GO molecular function (MF) enrichment analysis for nephrotoxicity targets demonstrated that the most highly enriched terms were protein binding (40 genes) and enzyme activity regulation (27 genes). The q-values for significantly enriched terms were all below 0.05, suggesting that the core toxic components of Naoxintong capsule primarily regulated nephrotoxicity-related targets by binding to target proteins and regulating target enzyme activities, representing a key molecular mechanism for component-mediated target function alteration (Figure 5).

The GO cellular component (CC) enrichment analysis showed that mitochondria (41 genes), plasma membrane (38 genes), and nucleus (35 genes) were the three most highly enriched cellular components with rich factor values all > 0.14. The results suggested that the nephrotoxic effects of Naoxintong capsule primarily occurred within these cellular structures (Figure 6). Mitochondria, as the center of cellular energy metabolism, had dysfunction as a key characteristic of drug-induced kidney injury, aligning well with the enrichment results of this study. In the GO functional enrichment analysis, the high enrichment of biological processes such as the regulation of apoptosis and inflammatory responses aligned closely with the pathological mechanisms of kidney injury. Excessive renal cell apoptosis led to damage of the renal

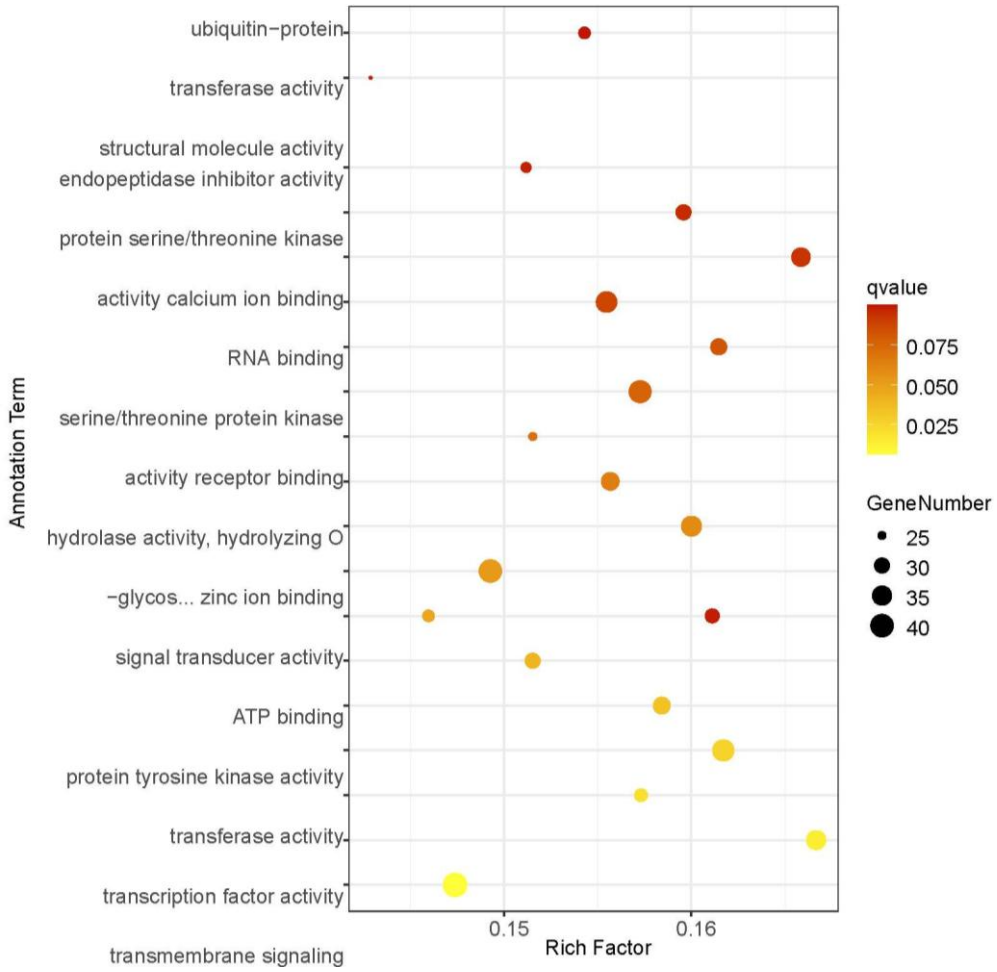

Figure 5. GO FE analysis of nephrotoxicity targets for Naoxintong capsule (top 20 MF items).

parenchyma, while persistent inflammation served as a key driving factor for renal fibrosis. The high enrichment of the PI3K-Akt signaling pathway in the KEGG results suggested that it might act as a core regulatory pathway in the nephrotoxicity process of Naoxintong capsule [18]. This pathway regulated cell survival and apoptosis, directly linked to core targets like AKT1. Its aberrant activation or inhibition could disrupt the homeostasis of renal cells. The enrichment of NF-κB and MAPK signaling pathways further confirmed the significant role of inflammatory responses in Naoxintong capsule nephrotoxicity. Regulation of these pathways by key components such as emodin and tanshinone IIA might trigger the cascade release of inflammatory factors like TNF, exacerbating renal tissue damage. The crosstalk between the PI3K-Akt and apoptosis pathways also underscored the complexity of the nephrotoxicity mechanism of Naoxintong capsule.

Molecular docking validation

The integrated molecular docking results for core active components and core nephrotoxicity targets showed that the binding affinity G-scores for all core toxic components with their corresponding targets were below -6.0 kcal/mol, indicating strong binding interactions and validating the molecular feasibility of component-target interactions predicted by the preceding network analysis (Table 2). In terms of interaction types, hydrogen bonds and hydrophobic interactions were the primary

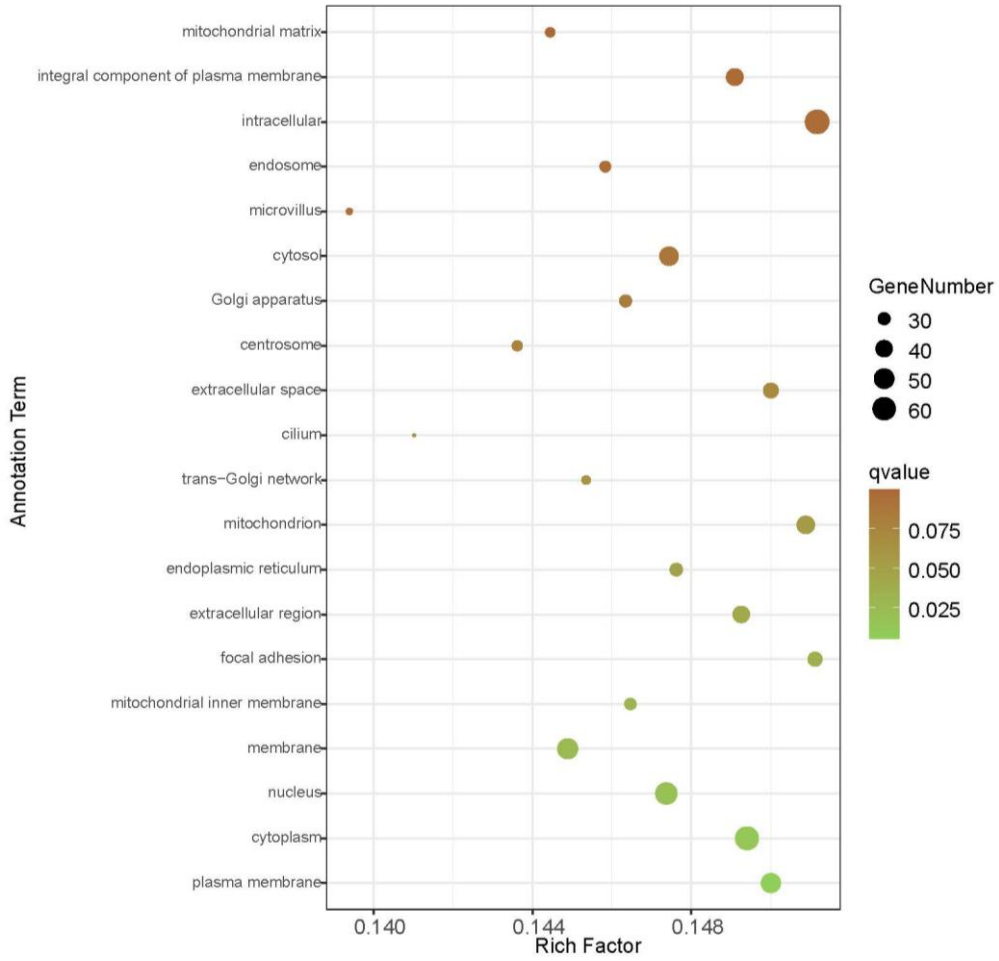

Figure 6. GO FE analysis diagram of nephrotoxicity targets for Naoxintong capsule (top 20 CC items).

Table 2. Ligand and receptor information for molecular docking.

Ligand information		Receptor information		
Mol ID	**Compound name**	**Gene name**	**Uniprot ID**	**PDB ID**
1	Quercetin	AKT1	P31749	3QKK
2	Kaempferol	TNF	P01375	2AZ5
3	Emodin	CASP3	P42574	4H10
4	Tanshinone IIA	EGFR	P00533	4HJO
5	Isorhamnetin	TP53	P04637	1TUP
		CASP3	P42574	4H10
		AKT1	P31749	3QKK
		TNF	P01375	2AZ5
		EGFR	P00533	4HJO
		TP53	P04637	1TUP
		AKT1	P31749	3QKK

forces for all component-target bindings. Hydrogen bonds stabilized the complex conformation by interacting with specific amino acid residues, while hydrophobic interactions

further enhanced binding stability, providing a structural basis for components to regulate target functions. The binding G-score for quercetin with AKT1 was -8.2 kcal/mol, the lowest among all docking combinations. The core binding sites were the Thr291 and Glu278 amino acid residues of AKT1. Quercetin formed stable hydrogen bonds with these residues, while hydrophobic interactions created spatial encapsulation around the active pocket. This binding characteristic enabled quercetin to efficiently bind AKT1 and modulate its activity [19]. As the core kinase of the PI3K-Akt pathway, aberrant AKT1 activity directly disrupted the balance between renal cell survival and apoptosis, suggesting quercetin might induce renal cell apoptosis by targeting AKT1 and mediating PI3K-Akt pathway dysregulation. The binding G-score for quercetin with TNF was -7.8 kcal/mol with primary binding sites at the Tyr119 and Pro120 residues of TNF. Hydrogen bonds and hydrophobic interactions jointly maintained binding stability. TNF was a central mediator of the inflammatory response. Strong binding of quercetin to TNF could directly inhibit its activity or block its interaction with receptors, thereby regulating the NF-κB inflammatory signaling pathway. This result corroborated the high enrichment of the NF-κB pathway in the preceding KEGG enrichment analysis, confirming quercetin as a core component mediating the inflammatory response in Naoxintong capsule nephrotoxicity. The G-score for kaempferol with EGFR was -7.5 kcal/mol. Binding sites were the Lys721 and Glu722 residues of EGFR with hydrogen bonds being the primary binding force. EGFR was a key target in cell proliferation and signal transduction. Its aberrant activation in renal tissue could exacerbate kidney injury. The specific binding of kaempferol to EGFR could regulate its downstream signaling pathways, representing a significant pathway for its nephrotoxic effects. The binding G-score for kaempferol with TP53 was -6.5 kcal/mol, which was achieved through hydrogen bond formation with the Arg248 residue of TP53. As a core regulator of apoptosis, TP53 activation initiated apoptotic programs in renal cells. The targeted binding of kaempferol to TP53 provided a molecular basis for its regulation of renal cell apoptosis. The G-score for emodin with CASP3 was -6.8 kcal/mol. The binding sites were the Cys163 and His121 residues of CASP3, which were active site residues. Strong binding of emodin to these sites could directly inhibit the protease activity of CASP3, a key executioner enzyme in apoptosis. Aberrant activity directly led to uncontrolled renal cell apoptosis, suggesting emodin might participate in the nephrotoxicity process of Naoxintong capsule by targeting and inhibiting CASP3 activity to regulate the apoptosis pathway. The G-score for emodin with AKT1 was -6.6 kcal/mol, further confirming its involvement in the nephrotoxicity mechanism through multi-target regulation. The G-score for tanshinone IIA with TNF was -6.5 kcal/mol with the binding site at the Asp143 residue of TNF, primarily involving hydrophobic interactions. This binding might synergize with quercetin to regulate TNF-mediated inflammatory responses, establishing tanshinone IIA as a key regulatory component in inflammatory pathways. The G-score for tanshinone IIA with EGFR was -6.3 kcal/mol, which was achieved through hydrophobic interactions with the Met769 residue of EGFR. This binding might synergize with kaempferol in regulating EGFR-mediated signaling pathways, exemplifying the synergistic action characteristic of multi-component TCM compounds [20]. The binding G-scores for isorhamnetin with TP53 and AKT1 were -6.2 kcal/mol and -6.0 kcal/mol, respectively. Although slightly lower than those of other core components, they still indicated strong binding. Its binding site with TP53 was the Lys120 residue, while with AKT1 was the Ala230 residue. Isorhamnetin might participate in regulating apoptosis and survival pathways through weaker modulation, acting as an auxiliary regulatory component in Naoxintong capsule nephrotoxicity (Table 3). Molecular docking validation provided evidence at the atomic level for the specific interactions between core toxic components of Naoxintong capsule and core nephrotoxicity targets, offering direct molecular interaction evidence for the multi-component synergistic

regulation of core target-pathways in its nephrotoxicity mechanism [21]. The synergistic regulation of the same target by different components and the cross-regulation of multiple targets by a single component further illustrated the multi-component, multi-target, multi-pathway toxicity characteristics of TCM compounds and explained the complexity of their nephrotoxicity mechanisms [22]. Furthermore, the molecular docking results of this study provided important references for subsequent *in vitro* experimental studies, offering scientific guidance for selecting concentrations of candidate toxic components and directions for validating core targets.

Table 3. Molecular docking results.

Gene name	Compound name	G-score
AKT1	Quercetin	-8.2
TNF	Quercetin	-7.8
CASP3	Quercetin	-7.0
EGFR	Kaempferol	-7.5
TP53	Kaempferol	-6.5
CASP3	Emodin	-6.8
AKT1	Emodin	-6.6
TNF	Tanshinone IIA	-6.5
EGFR	Tanshinone IIA	-6.3
TP53	Isorhamnetin	-6.2
AKT1	Isorhamnetin	-6.0

Conclusion

The potential mechanism of nephrotoxicity induced by Naoxintong capsule was systematically studied by the network pharmacology method. By fabricating a multi-dimensional CTP network, the potential material basis and molecular pathway of nephrotoxicity were revealed. The results showed that various active components in Naoxintong capsule might act synergistically on several core targets and induce nephrotoxicity by regulating key biological processes such as apoptosis and interfering with signaling pathways closely related to renal injury including PI3K-Akt, MAPK, and NF-κB. The results provided a mechanism explanation for the potential renal safety risks related to its clinical application. However, this research relied on database mining and computational simulation, and its findings needed to be further verified. In addition, the complex metabolic process of drugs *in vivo* and the interaction between components had not been fully considered, which represented the limitations of this study. Future research should integrate experimental pharmacology and clinical data, thoroughly verify the toxic effect of core components and their dose-toxicity relationship, and explore strategies to reduce the risk of nephrotoxicity through compatibility optimization or personalized medication, thereby laying a more solid scientific basis for safe adoption of Naoxintong capsule.

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