

Identification of Key Targets for Proton Pump Inhibitors Induced Tubulointerstitial Nephritis Based on Pharmacovigilance and Network Toxicology Analysis

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Abstract: *Objective:* Although previous studies have demonstrated that proton pump inhibitors (PPIs) can induce tubulointerstitial nephritis (TIN), the specific mechanism of action remains incompletely understood. *Methods:* We integrated data from Q1 2004 to Q4 2025 in the FAERS database; the associations between PPIs and TIN were quantified by four disproportionality algorithms. The potential targets for PPIs-induced TIN were identified by combining network toxicology and protein-protein interaction networks. Moreover, molecular docking between key targets and PPIs was conducted. *Results:* Five PPIs had significantly associated with TIN: lansoprazole (ROR = 49.13, 95% CI = 46.51-51.90), pantoprazole (ROR = 33.71, 95% CI = 31.73-35.82), dexlansoprazole (ROR = 32.39, 95% CI = 27.86-37.65), omeprazole (ROR = 30.12, 95% CI = 28.45-31.88), and esomeprazole (ROR = 26.77, 95% CI = 25.58-28.02). Three key targets for PPI-induced TIN were determined: CDC42, PDGFRA, and MAPK8. Among these targets, the binding between CDC42 and esomeprazole was the most stable (binding energy: -7.44 kcal/mol). *Conclusion:* These findings suggest that PPIs may trigger TIN through multi-target interactions. This study provides potential mechanistic clues and novel targets for the early warning and precise intervention of PPI-related kidney injury.

Keywords: FAERS; Proton pump inhibitors; Tubulointerstitial nephritis; Network toxicology; Key target

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1. Introduction

Tubulointerstitial nephritis (TIN) is a main cause of kidney impairment, characterized by a diverse range of etiologies. Clinically, it is generally categorized into acute and chronic forms ^[1]. This disease is marked by inflammation in the interstitial tubular area of the kidney, frequently associated with a swift decline in kidney

function, exhibiting a clinical trajectory akin to acute kidney injury (AKI), and representing approximately 20% of chronic kidney disease (CKD) ^[2,3]. Adverse reactions to medicines—particularly antibiotics, nonsteroidal anti-inflammatory drugs (NSAID), and proton pump inhibitors (PPIs)—as well as infections, are the predominant catalysts for TIN ^[4,5]. Drug-induced adverse reactions and infections are the primary causes of TIN, with drug-related cases (particularly those involving antibiotics, NSAID, and PPIs) accounting for over 75% of all cases ^[6]. Among these, PPIs—including omeprazole, esomeprazole, lansoprazole, pantoprazole, dexlansoprazole, and rabeprazole—are widely prescribed for acid-related disorders. However, despite their extensive use and established association with severe kidney outcomes (e.g., acute interstitial nephritis and acute kidney injury), the precise molecular mechanisms through which PPIs induce TIN remain poorly elucidated (Miao and Herrmann, 2023).

The FDA Adverse Event Reporting System (FAERS) database contains millions of adverse event reports linked to drugs, offering real-world clinical data and establishing itself as one of the largest pharmacovigilance databases globally ^[7,8]. Network toxicology methodologies provide an effective means for swiftly and efficiently elucidating the toxicological processes of drugs ^[9,10]. This research employed the FAERS database to conduct a systematic pharmacovigilance analysis aimed at identifying risk characteristics of TIN associated with PPIs. Subsequently, employing network toxicology methodologies, the potential targets of PPI-induced TIN were predicted. Our analysis aims to comprehensively elucidate the underlying molecular mechanisms by which PPIs induce TIN, providing scientific evidence for clinical risk prevention and targeted interventions.

2. Materials and methods

2.1. Data source and processing

Adverse drug event (ADE) data linked to drug-induced TIN, with the drug designated as the primary suspect (PS), were retrieved from the FAERS database (<https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html>) spanning Q1 2004 through Q4 2025. The extracted datasets comprised seven standardized files: patient demographics (DEMO), adverse reaction (REAC), drug details (DRUG), patient outcomes (OUTC), report sources (RPSR), drug therapy start dates and end dates (THER), and prescribing indications (INDI) ^[11]. Duplicate entries were eliminated per FDA protocol, retaining the record with the latest FDA-DT when CASEIDs overlapped, and the larger PRIMARYID when both CASEID and FDA-DT matched ^[12]. Drug nomenclature was harmonized using RxNorm, while ADEs were classified by mapping MedDRA® (version 27.1) system organ class (SOC) and preferred terms (PT) codes to Standardized MedDRA Queries (SMQs). Personal information, event outcomes, drug indications, and drug-related data were extracted from adverse event reports linked to “TUBULOINTERSTITIAL NEPHRITIS”, eliminating reports where the indication is “TUBULOINTERSTITIAL NEPHRITIS”. The whole study design flowchart is presented in **Figure 1**.

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies ^[13].

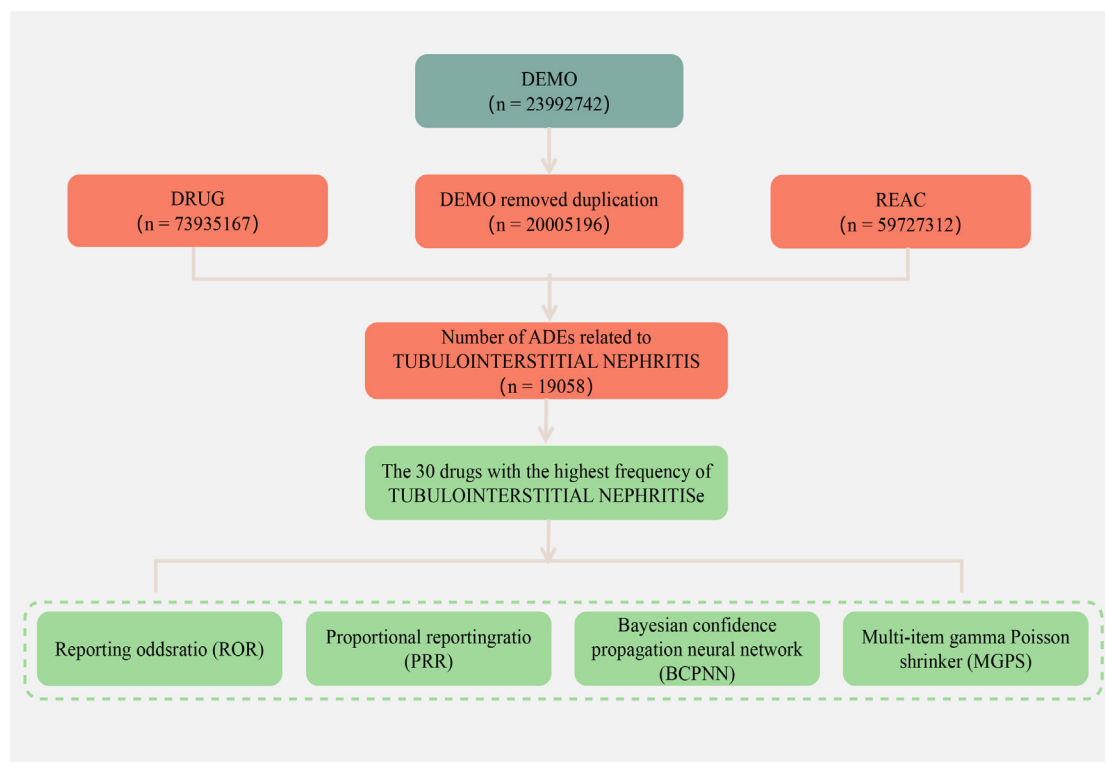


Figure 1. The flow-process diagram of tubulointerstitial nephritis (TIN) from FAERS database.

2.2. Disproportionality analysis

To evaluate potential links between TIN and pharmacological agents, four distinct disproportionality metrics were deployed: reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS) ^[14]. Each algorithm operated on a standard 2×2 contingency matrix. Signal detection thresholds required: minimum report count of 3, ROR lower 95% confidence interval (CI) exceeding 1, $PRR \geq 2$, $\chi^2 \geq 4$, $IC_{025} > 0$, and $EBGM_{05} > 2$. Elevated ROR magnitudes suggest more pronounced associations, though such quantitative associations remain pharmacovigilance hypotheses rather than confirmed pathophysiological causation.

2.3. Target selection of drugs and TIN

For mechanistic exploration, drug-specific protein targets were computationally inferred via SwissTarget and TargetNet platforms. Disease-relevant molecular entities associated with TIN were mined from OMIM, STRING, and GENECARDS repositories using standardized disease nomenclature. The intersection of targets for both drugs and TIN was derived to pinpoint candidate genes. To investigate the functional impact and processes of candidate genes, enrichment analyses for GO and KEGG were performed utilizing the “clusterProfiler” package (version 4.6.2), with a significance threshold of adjusted $p < 0.05$ ^[15]. Finally, the drug-target-disease network was constructed.

2.4. Identification of key genes in TIN

A functional protein interaction map for candidate genes was generated via STRING (confidence score > 0.4). Topological prioritization leveraged six distinct centrality metrics—BottleNeck, MCC, EcCentricity, DMNC,

Degree, and ClusteringCoefficient—to extract the 20 highest-ranking nodes from each analytical framework. Genes consistently emerging across all 6 ranking schemes were designated as key genes. Subsequently, an integrative visualization depicting drug-key genes-KEGG pathways was assembled and rendered using Cytoscape.

2.5. Molecular docking

To understand the interactions of key genes with corresponding drugs, the 3D structures of drugs (SDF files) were obtained from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) and converted into PDB format using the Babel GUI. The 3D structural coordinates for proteins encoded by key genes were retrieved from the UniProt database (<https://www.uniprot.org/>). Prior to docking simulations, structural preprocessing—specifically elimination of crystallographic waters and dissociated low-molecular-weight ligands—was executed in AutoDock software (version 1.1.2) ^[16]. Then, molecular docking analysis was performed through AutoDock and visualized by PyMol.

2.6. Molecular dynamics (MD) simulation

All-atom simulations were executed in Gromacs 2022. Parameterization of ligands employed the GAFF force field, whereas macromolecular and aqueous phases were described by AMBER14SB and TIP3P, respectively. Covalent bonds involving hydrogen were constrained through the LINCS algorithm, enabling a 2-femtosecond integration timestep. Extended-range Coulombic interactions were computed via the Particle-mesh Ewald method with a 1.3-nm cutoff; van der Waals and short-range electrostatic cutoffs were set to 10 Å and updated every 10 steps. Temperature regulation at 298 K was achieved through the V-rescale thermostat, while pressure maintenance at 1 bar utilized Berendsen coupling. Following 100-ps equilibration under both NVT and NPT ensembles, a 100-nanosecond production trajectory was propagated, with atomic coordinates archived at 10-ps intervals. Trajectory post-processing and visualization leveraged VMD and PyMOL. Binding affinities were quantified through the g_mmpbsa approach. Conformational and interaction metrics—including root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), Hbond, and solvent accessible surface area (SASA)—were extracted and evaluated.

2.7. Toxicity analysis

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) of compounds were profiled through the SwissADME database (<http://www.swissadme.ch/>). Toxicological forecasting was subsequently performed via ProTox-III database (<https://tox.charite.de/prottox3/>).

2.8. Statistical analysis

All computational statistics were executed in R software (version 4.2.1). A *P*-value below 0.05 was considered significant.

3. Results

3.1. Descriptive characteristics

Between Q1 2004 and Q4 2025, the FAERS repository yielded 19,058 ADE records linked to TIN. **Table 1** delineated the demographic characteristics of this cohort. Regarding gender distribution, the percentage

of males (42.2%) was higher than that of females (38.8%). Age-stratified analysis revealed the highest case density within the 18-to-64-year bracket (n = 7,535, 39.5%). Most reports were submitted by physicians (n = 5,565, 29.2%), followed by other health professionals (n = 2,958, 15.5%). Outcome-wise, the dominant clinical endpoint fell under the “other serious outcomes” rubric (OT), capturing 7,302 instances or 38.3% of the total. Hospitalization (HO) (n = 6,762, 35.5%) constituted the next most frequent category. Otherwise, the top 5 reported countries of ADEs for TIN were the United States (n = 8,583, 45.0%), France (n = 1,564, 8.2%), Japan (n = 1,520, 8.0%), the United Kingdom (n = 1,260, 6.6%), and Spain (n = 682, 3.6%) (**Figure 2A**). From 2004 to 2024, the peak of reports was in 2018 (n = 2,528, 13.3%), and the second year was 2019 (n = 2,491, 13.1%) (**Figure 2B**).

Table 1. Clinical characteristics of patients with adverse drug events (ADEs) of tubulointerstitial nephritis (TIN)

Characteristics	Variable	Number of reports	percentage
Gender	Overall (N = 19,058)		
	Female	7,394	38.8%
	Male	8,044	42.2%
	Unknown	3,620	19.0%
Age	< 18	1,014	5.3%
	18–64	7,535	39.5%
	65–85	5,121	26.9%
	> 85	324	1.7%
	Unknown	5,064	26.6%
Reporter’s occupation	Consumer (CN)	2,020	10.6%
	Health professional (HP)	2,788	14.6%
	Lawyer (LW)	1,471	7.7%
	Physician (MD)	5,565	29.2%
	Other health professional (OT)	2,958	15.5%
	Pharmacist (PH)	1,513	7.9%
Reported time	Unknown	2,742	14.4%
	2004	290	1.5%
	2005	314	1.6%
	2006	357	1.9%
	2007	341	1.8%
	2008	295	1.5%
	2009	351	1.8%
	2010	338	1.8%
	2011	371	1.9%
	2012	466	2.4%
	2013	507	2.7%
	2014	590	3.1%
	2015	467	2.5%
	2016	666	3.5%
	2017	668	3.5%
	2018	2,528	13.3%
	2019	2,491	13.1%

Characteristics	Variable	Number of reports	percentage
Outcome	2020	1,414	7.4%
	2021	1,572	8.2%
	2022	1,228	6.4%
	2023	1,300	6.8%
	2024	1,195	6.3%
	2025	1,309	6.9%
	Death (DE)	993	5.2%
	Disability (DS)	127	0.7%
	Hospitalization (HO)	6,762	35.5%
	Life -threatening (LT)	844	4.4%
	Other serious outcomes (OT)	7,302	38.3%
	Required intervention (RI)	18	0.1%
	Missing	3,009	15.8%

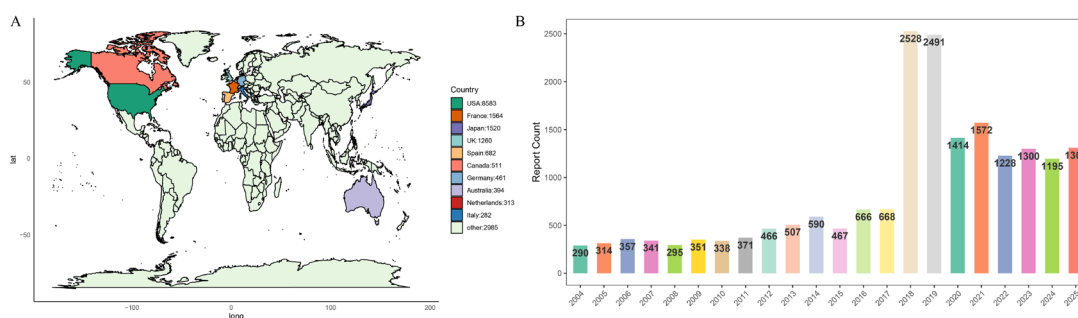


Figure 2. Signal detection for TIN. (A) Country distribution of reports for TIN. (B) Distribution of reports for TIN from 2004 to 2025.

3.2. Drug selections associated with TIN

Through pharmacovigilance signal mining, t30 pharmaceutical agents emerged as the most frequently implicated culprits in TIN pathogenesis (**Figure 3**). These drugs included esomeprazole (n = 2,089), lansoprazole (n = 1,398), omeprazole (n = 1,276), pantoprazole (n = 1,125), and ibuprofen (n = 780). Of this prioritized pharmaceutical cohort, 27 agents exhibited statistically significant disproportionality signals, and lansoprazole had the highest interactions with TIN (ROR = 49.13 95% CI = 46.51-51.90). The rising utilization of PPIs has heightened the risk of TIN ^[17], promoting our focus on the drugs of PPIs: lansoprazole (ROR = 49.13, 95% CI = 46.51-51.90), pantoprazole (ROR = 33.71, 95% CI = 31.73-35.82), dexlansoprazole (ROR = 32.39, 95% CI = 27.86-37.65), omeprazole (ROR = 30.12, 95% CI = 28.45-31.88), and esomeprazole (ROR = 26.77, 95% CI = 25.58-28.02), which were also the top 5 drugs with positive signals and the higher ROR value for subsequent analysis.

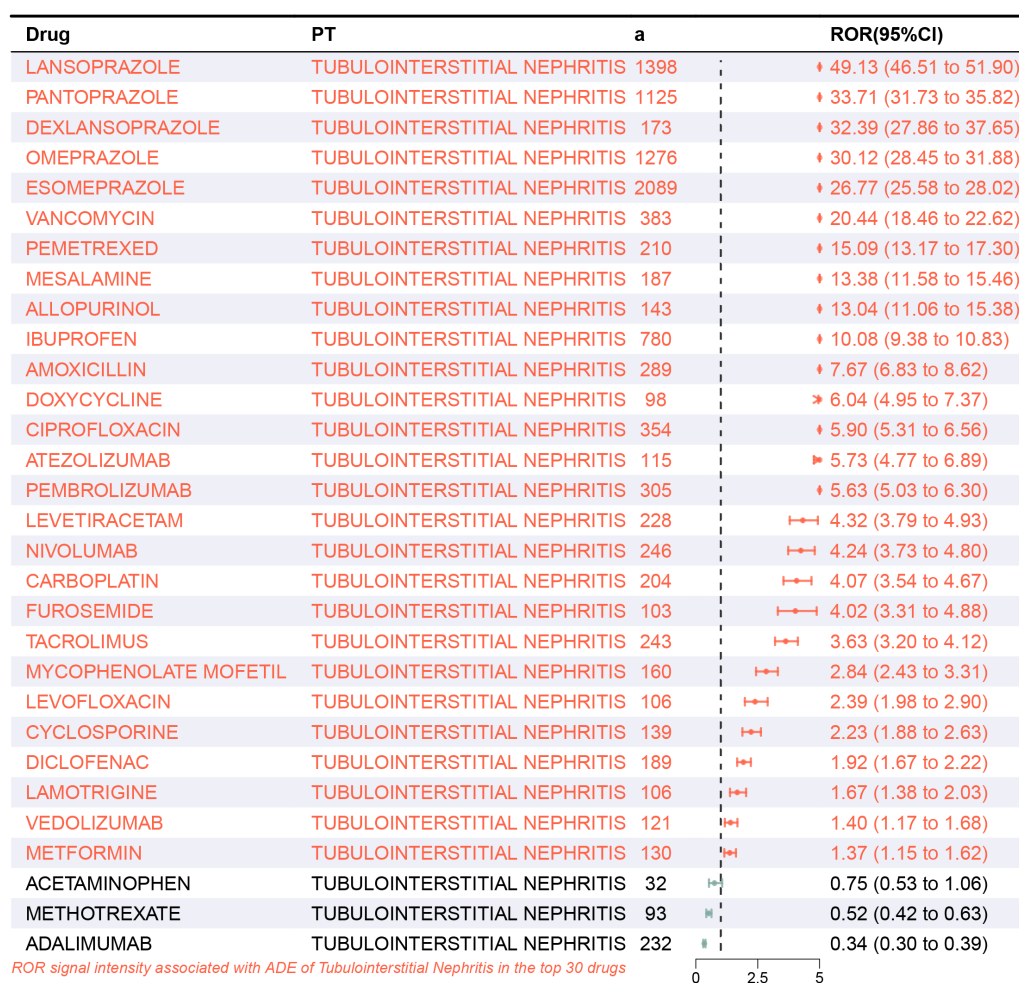


Figure 3. The forest plot for top 30 drugs caused TIN.

3.3. Pharmacological properties of PPIs

In silico ADMET characterization of the five prioritized compounds was undertaken to profile their biopharmaceutical attributes. Tabulated data reveal pronounced intestinal permeability coupled with negligible blood-brain barrier penetration, implying restricted central nervous system distribution. Additionally, each agent exhibited P-glycoprotein substrate liability alongside inhibitory potential against major hepatic CYP isoforms, notably CYP1A2, CYP2C19, CYP2D6, and CYP3A4. The log K_p value of these drugs ranged from -6.42 cm/s to -6.96 cm/s. Additionally, the toxicity of these drugs was also explored, and their predicted lethal dose (LD) was 1,400 mg/kg, and the toxicity class was 4, which indicated that these drugs were moderately toxic.

3.4. Identification and function prediction of shared targets between drugs and TIN

After summarizing and removing duplication, 252 drug-related targets and 1,024 TIN-related targets were obtained from the corresponding databases. The intersection of these targets yielded 44 candidate genes (**Figure 4A**). To explore the functions of these candidate genes in disease, enrichment analyses were

conducted, revealing 1,325 GO terms, including phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signal transduction, membrane raft, and protein tyrosine kinase activity, and 141 KEGG pathways such as AGE-RAGE signaling pathway in diabetic complications and Endocrine resistance (**Figure 4B**). Furthermore, PPI network of candidate genes was developed with 44 nodes and 390 interaction pairs (**Figure 4C**). Among this network, AKT1 had the most correlations with other genes, such as SIRT1, MAPK1, and PDGFRA. Additionally, a candidate gene-drug-TIN regulatory network was established with 50 nodes and 163 edges. In this network, five drugs targeted ATP4A, DNMT1, FYN, HNF4A, S1PR2, TEK, and TLR9 (**Figure 4D**).

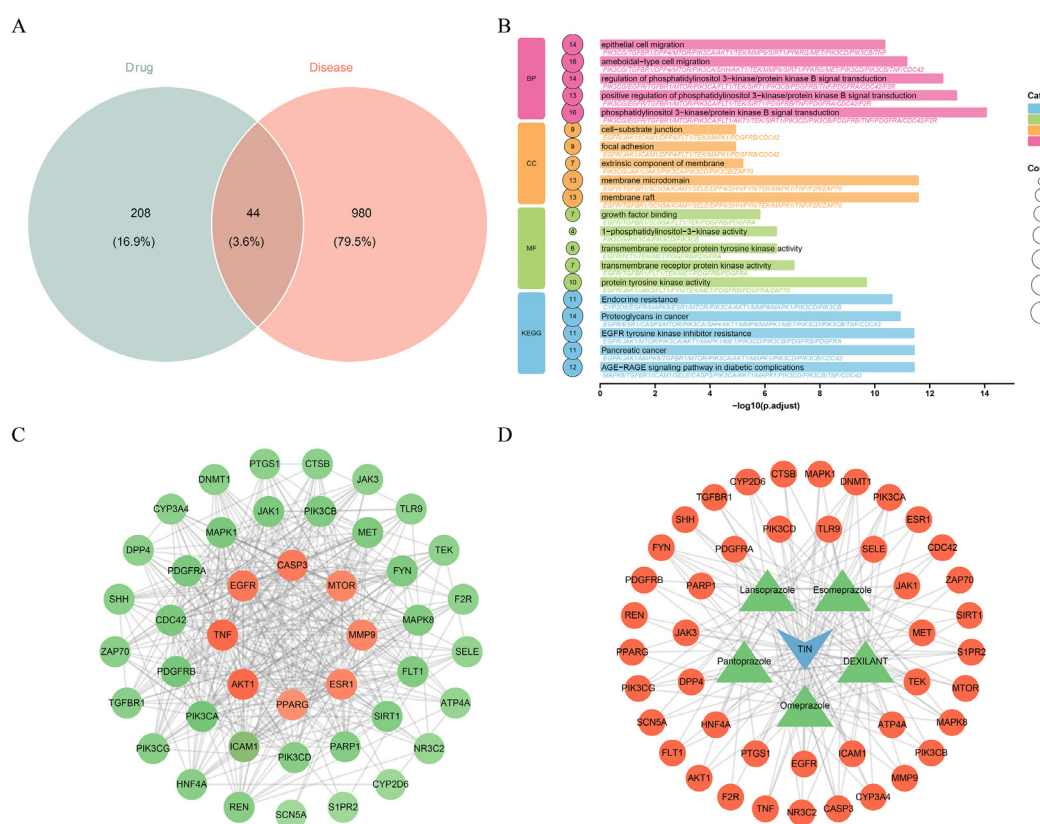


Figure 4. Identification of candidate genes in TIN. (A) The intersection of drugs and TIN-related targets. (B) The enrichment analysis of candidate genes. (C) The interactions of candidate genes at the protein level. (D) The regulatory network of candidate gene-drug-TIN. Green represents drugs; orange denotes candidate genes.

3.5. CDC42, PDGFRA, and MAPK8 were identified as key genes in TIN

Topological prioritization of the candidate gene interactome employed 6 centrality metrics—BottleNeck, MCC, EcCentricity, DMNC, Degree, and ClusteringCoefficient—to extract the 20 foremost nodes per algorithm. The convergent subset across all 6 ranking schemes comprised 3 consensus molecules: CDC42, PDGFRA, and MAPK8, designated as the key genes (**Figure 5A**). Leveraging these pivotal targets, an integrative tripartite network was assembled, encompassing 96 vertices and 119 connections, linking pharmaceutical agents, key genes, and KEGG-annotated pathways (**Figure 5B**). Within this architecture, omeprazole and esomeprazole converged upon PDGFRA and MAPK8, both implicated in focal adhesion

dynamics. Lansoprazole, meanwhile, engaged MAPK8 within the T-cell receptor signaling cascade. Subsequent in silico binding simulations between these core genes and their respective ligands yielded favorable thermodynamic profiles, with all affinity estimates falling below -5 kcal/mol (**Table 2**). As shown in **Figure 5C**, omeprazole and esomeprazole correlated with CDC42 residues ALA-159, ASP-118, and GLN-116. Lansoprazole was associated with MAPK8 residues CYS-245, LEU-241, and GLY-242; omeprazole with residues ASN-114, ILE-32, and MET-111; esomeprazole with residues MET-111 and LYS-55; while dexlansoprazole with residues LEU123 and MET-218. Furthermore, omeprazole correlated with PDGFRA residues LEU-599 and ASP-681; pantoprazole with PDGFRA residues ARG-558 and ARG-554; while esomeprazole correlated with residues GLN-619, TYR-676, and LYS-623.

Figure 5. CDC42, PDGFRA, and MAPK8 were identified as key genes in TIN. **(A)** The selection of key genes by 6 algorithms. **(B)** The regulatory network of drug-key gene-pathway. Orange represents key genes, blue denotes drug, and green represents pathways. **(C)** Molecular docking analysis between drugs with key genes.

Table 2. The molecular docking of key genes with drugs

Key genes	UniProt	PDB	Drugs	CID	Binding energy (kcal/mol)	Number of hydrogen
CDC42	P60953	1AN0	Omeprazole	CID4594	-7.335	3
CDC42	P60953	1AN0	Esomeprazole	CID9568614	-7.44	3
MAPK8	P45983	2XS0	Lansoprazole	CID3883	-5.53	4
MAPK8	P45983	2XS0	Omeprazole	CID4594	-6.1	3
MAPK8	P45983	2XS0	Esomeprazole	CID9568614	-7.15	3
MAPK8	P45983	2XS0	Dexlansoprazole	CID9578005	-5.88	4
PDGFRA	P16234	8PQJ	Omeprazole	CID4594	-6.99	4
PDGFRA	P16234	8PQJ	Pantoprazole	CID4679	-6.06	4
PDGFRA	P16234	8PQJ	Esomeprazole	CID9568614	-6.72	4

3.6. CDC42-esomeprazole compound had a stable structure

Collectively, these orthogonal lines of evidence affirm a robust and stable CDC42–esomeprazole interaction.

Tabulated data in **Table 2** identified the CDC42-esomeprazole pairing as exhibiting the most favorable thermodynamic signature (-7.44 kcal/mol), prompting MD simulation of this complex. Trajectory interrogation across the 100-ns production run evidenced structural equilibration, as gauged by RMSD, RMSF, and Rg (**Figure 6A-C**). Intermolecular hydrogen-bond occupancy oscillated between zero and four throughout the simulation window (**Figure 6D**). The SASA variability reflected ongoing conformational sampling; notably, Buried SASA remained non-0, signifying persistent interfacial contact and complex integrity (**Figure 6E**). Finally, their ΔE_{MMPBSA} value was -80.026 ± 10.403 kJ/mol, corroborating pronounced ligand–receptor affinity. Collectively, these orthogonal lines of evidence affirm a robust and stable CDC42–esomeprazole interaction.

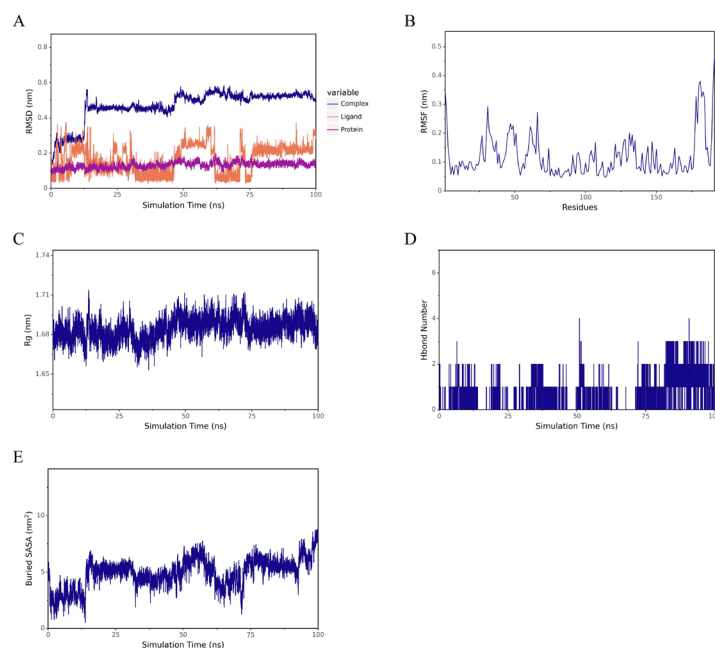


Figure 6. Molecular dynamics analysis of CDC42-esomeprazole compound. (A-C) The results of root mean square deviation (RMSD) (A), root mean square fluctuation (RMSF) (B), and radius of gyration (Rg) (C) for the CDC42-esomeprazole compound. (D) The number of H-bonds. (E) The Buried solvent accessible surface area (SASA) result.

4. Discussion

Previous studies indicate a substantial correlation between PPIs and kidney illnesses such as AKI and CKD^[18]. Hart E *et al.* discovered that PPIs can elevate the chance of AKI development by as much as sixfold, while Al-Aly Z *et al.* established a robust correlation between PPI use and heightened risk of CKD initiation and progression^[19]. In this study, five PPI drugs showed the strongest association with TIN: lansoprazole (ROR = 49.13, 95% CI = 46.51–51.90), pantoprazole (ROR = 33.71, 95% CI = 31.73–35.82), dexlansoprazole (ROR = 32.39, 95% CI = 27.86–37.65), omeprazole (ROR = 30.12, 95% CI = 28.45–31.88), and esomeprazole (ROR = 26.77, 95% CI = 25.58–28.02). Among these drugs, omeprazole was found to induce oxidative stress and apoptosis in kidney tubular cells via mechanisms including membrane-associated protein V/7-AAD staining, LDH release, abnormal chromatin condensation, and vesicle formation, resulting in kidney injury^[20]. Lansoprazole, specially, influences regulatory mechanisms in AIN by altering T-cell immunological responses^[21]. At present, there is inadequate evidence about the role of alternative drugs in TIN. Nonetheless, current research indicates that PPIs can activate host immune responses via semi-antigenisation (by binding to larger host proteins to gain immunogenicity) or through direct interactions with immune receptors or major histocompatibility complex (MHC) proteins (pharmacological interactions)^[22]. The accumulation of PPIs and their metabolites in interstitial spaces, together with subsequent immunological reactions, may be potential underlying causes of the illness^[23]. Lesions in the tubulointerstitium can precipitate a swift decline in kidney function and exacerbate AKI, attributed to chronic interstitial nephritis (CIN), finally culminating in kidney failure and, in severe instances, CKD^[24]. These findings further confirm that PPIs are not only associated with kidney injury in a broad sense, but also that their specific risk of inducing TIN varies between drugs and may drive disease progression through shared immune-inflammatory pathways.

Subsequently, network toxicology analysis further identified three potential targets (CDC42, PDGFRA, and MAPK8) for PPI-induced TIN. Existing research indicates that these three targets are involved in regulating crucial pathophysiological processes, including cytoskeletal reorganization and tubular morphogenesis, tissue repair and fibrosis progression, as well as inflammatory responses and apoptosis, thereby playing pivotal roles in renal injury. Specifically, the ablation of CDC42 markedly diminishes the expression of α -SMA, fibronectin, and type I collagen in kidney fibroblasts, concurrently inhibiting the pathways that facilitate fibroblast activation^[25]. Recent findings indicate that CDC42 is predominantly expressed in kidney tubules and the kidney tubular interstitium, significantly influencing kidney tubule formation through the regulation of cytoskeletal dynamics. Inhibition of CDC42 markedly reduces kidney tubular injury, encompassing significant vacuolization, granular degeneration, epithelial cell flattening, and lumen dilatation^[26]. In the study by Toda N *et al.*, PDGFRA was shown to be expressed in multiple renal cell types, including collecting duct cells, proximal tubular cells, and interstitial fibroblasts^[27]. Moreover, in CKD mice, hedgehog signaling was observed to enhance PDGFRA expression and promote the development of new endothelium in arteriovenous fistulas^[28]. In ischemia-reperfusion-induced acute kidney damage, MAPK8 is markedly activated in kidney tissue, and the inhibition of MAPK8 diminishes tubular necrosis and inflammatory infiltration^[29]. Furthermore, Bruno S *et al.* discovered that the activation of the MAPK8-mediated pathway is involved in both G2/M arrest and apoptosis of kidney tubular epithelial cells, while also enhancing the expression of TGF- β 1 and CTGF in G2/M-arrested kidney tubular cells. These results in aberrant repair of kidney tubular epithelial cells, increased collagen production, and the facilitation of fibrosis progression^[30,31]. However, the specific molecular pathways by which PPIs act on these targets to initiate

immune-inflammatory responses and cause tubulointerstitial injury remain unclear. Future experimental investigations are required to better substantiate the regulatory functions of these targets and their upstream and downstream signaling networks in PPI-associated TIN, thereby providing more direct evidence for elucidating its pathogenic mechanisms.

In silico binding predictions between the prioritized gene set and corresponding ligands identified the CDC42–esomeprazole association as the most thermodynamically favorable, registering a minimum affinity estimate of -7.44 kcal/mol. This optimal complex was subsequently advanced to explicit-solvent molecular dynamics. MD analysis—encompassing RMSD, RMSF, and Rg—corroborated sustained conformational integrity throughout the simulated interval. Esomeprazole is a type of PPI that can be efficiently utilized in the clinical management of peptic ulcers and associated conditions, providing benefits such as enhanced metabolic stability and increased bioavailability^[32]. This interaction provides structural evidence for understanding how PPIs disrupt cytoskeletal regulation through specific molecular interactions, potentially driving renal tubulointerstitial injury. Molecular dynamics simulations reveal the dynamic behavior of protein-drug complexes at the atomic level, aiding in elucidating the potential origins of PPI-related nephrotoxicity at the mechanistic level^[33].

By integrating the FAERS database with network toxicology, this study for the first time systematically identified potential molecular targets (CDC42, PDGFRA, and MAPK8) for PPI-induced TIN, thereby advancing the mechanistic understanding of PPI-related nephrotoxicity and offering new leads for targeted intervention. Nonetheless, our study possesses specific limitations. Reports submitted to FAERS are voluntary in nature, which introduces inherent limitations including incomplete capture of adverse events, temporal lags in documentation, and information gaps. Moreover, investigations leveraging this pharmacovigilance repository for safety profiling remain observational in design, thereby precluding the establishment of definitive causality between the investigated therapeutic agents and TIN. Ultimately, although network pharmacology and bioinformatics investigations have pinpointed key targets for PPI-induced TIN, the specific pathogenic mechanisms remain to be fully elucidated. Subsequent basic experiments are required to validate these key targets and further clarify the specific pathogenic mechanisms of PPI-related TIN.

5. Conclusion

This study further substantiates the high correlation between PPIs and TIN through FAERS database, revealing differential risks among different PPI drugs, particularly lansoprazole. By integrating network toxicology and molecular docking simulations, the study systematically identified potential key targets such as CDC42, PDGFRA, and MAPK8 for the first time, providing new directions for elucidating the molecular mechanisms underlying PPI-induced TIN. These findings suggest that clinical practice should strengthen early renal function monitoring during PPI use, particularly for high-risk formulations, and lay a theoretical foundation for developing targeted intervention strategies. Despite inherent limitations of spontaneous reporting databases, the multidimensional analytical approach provides crucial insights for understanding the mechanisms and prevention of drug-induced kidney injury.

Data availability statement

Adverse drug events (ADEs) data used in this study were downloaded from the FAERS database (<https://>

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Disclosure statement

The authors declare no conflict of interest.

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