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The molecular mechanisms of peptidyl-prolyl *cis/trans* isomerase Pin1 and its relevance to kidney disease

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Pin1 is a member of the peptidyl-prolyl cis/trans isomerase subfamily and is widely expressed in various cell types and tissues. Alterations in Pin1 expression levels play pivotal roles in both physiological processes and multiple pathological conditions, especially in the onset and progression of kidney diseases. Herein, we present an overview of the role of Pin1 in the regulation of fibrosis, oxidative stress, and autophagy. It plays a significant role in various kidney diseases including Renal I/R injury, chronic kidney disease with secondary hyperparathyroidism, diabetic nephropathy, renal fibrosis, and renal cell carcinoma. The representative therapeutic agent Juglone has emerged as a potential treatment for inhibiting Pin1 activity and mitigating kidney disease. Understanding the role of Pin1 in kidney diseases is expected to provide new insights into innovative therapeutic interventions and strategies. Consequently, this review delves into the molecular mechanisms of Pin1 and its relevance in kidney disease, paving the way for novel therapeutic approaches.

KEYWORDS

Pin1, fibrosis, oxidative stress, autophagy, kidney disease

1 Introduction

Kidney disease is an overarching term that encompasses a range of conditions resulting from diverse structural and functional damage to the kidneys, including acute kidney injury (AKI), chronic kidney disease (CKD), glomerular diseases, and diabetic nephropathy (DN) (Cavanaugh and Perazella, 2019; Luyckx et al., 2021). Due to challenges in early diagnosis and often overlooked symptoms, patients with kidney disease frequently progress to end-stage renal disease (ESRD), renal failure (RF), and a decline in renal function (Levey et al., 2003). The intricate pathogenesis of these conditions involves multiple molecular

mechanisms and signaling pathways. Current treatments primarily rely on prolonged drug therapy, chronic dialysis, and kidney transplantation (Himmelfarb et al., 2020; Yan et al., 2021). However, these approaches often fail to yield satisfactory results. Therefore, it is important to elucidate the underlying mechanisms that contribute to the onset and progression of kidney disease to explore effective preventive and treatment interventions (O Toole and Sedor, 2014).

The functional properties of a protein are associated with its native-state topology, corresponding post-translational modifications, and signal-induced structural rearrangements (Matena et al., 2018). The cis/trans isomerization of peptide bonds involving any proteogenic amino acid, (Xaa)-Pro, is a rate-limiting step during protein structural rearrangements (Brandts et al., 1977). Peptidyl-proline isomerases (PPIases), which act as molecular switches, have previously been identified as participants in the acceleration of cis/trans isomerization. This process plays a crucial role in deactivating or activating enzymes and facilitating protein-protein interactions (Lang et al., 1987; Fischer et al., 1989; Andreotti, 2003). PPIases constitute a superfamily of molecular chaperones categorized by distinct topological structures and folds, including cyclophilins (CYPs), FK506-binding proteins (FKBPs), parvulins, and protein phosphatase (PPase) 2A phosphatase activators (PTPA) (Fischer et al., 1998; Jordens et al., 2006; Davis et al., 2008; Zhou and Lu, 2016). These enzymes can catalyze the isomerization of polypeptide bonds and play a role in regulating protein folding and function. This regulation controls the biological activities of numerous proteins and has been implicated in a wide range of diseases (Schmid, 1993; Fischer et al., 1998; Galat, 2003; Cao and Konsolaki, 2011; Nigro et al., 2013).

Pin1, also known as Protein NIMA 1, is an 18 kDa protein that belongs to the parvulin subfamily (Zhao et al., 2016). Numerous studies have demonstrated that Pin1-mediated isomerization plays a pivotal role in various biological processes, including the cell cycle, cell proliferation, apoptosis, signal transduction, transcription and splicing, immune response, and maintenance of the cytoskeleton (Esnault et al., 2007; Yeh and Means, 2007; Akiyama et al., 2009; Zhang J. H. et al., 2022). Furthermore, dysregulation of Pin1 is closely linked to the onset and progression of various diseases. These include neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), as well as tumors, cardiometabolic diseases, and diseases related to viral infections (Sultana et al., 2006; Yeh and Means, 2007; Liang et al., 2018; Sun et al., 2020; Kato et al., 2022; Saeed and Piracha, 2023; Yang et al., 2023). Although the role of Pin1 in the aforementioned disorders have been extensively studied, its effect on kidney disease has received limited attention. Hence, we present a concise overview of Pin1, focusing on its structural biology and discussing the existing knowledge regarding its involvement in various kidney diseases.

2 Structure and biological function of Pin1

Lu et al. initially discovered that Ess1, the human ortholog of Pin1, serves as a regulatory protein involved in the growth, transcription, and mitosis of budding yeast (Hanes et al., 1989; Hani et al., 1995; Lu et al., 1996). Human *PIN1* is located on chromosome 19p13 and encodes a protein consisting of 163 amino acids (AAs) (Lu et al., 2009). Human Pin1 protein is a 163-AA peptidyl-coaminoyl cis/trans isomerase, consisting of an N-terminal WW (Trp-Trp) domain and a C-terminal PPIase domain with a central β-sheet (Figure 1) (Lu and Zhou, 2007; Nakatsu et al., 2016). These two domains are responsible for recognizing proteins containing phosphorylated Ser/Thr-Pro motifs and catalyzing cis-trans isomerization of the corresponding peptide bonds, respectively, forming a 'double-check mechanism' (Lu et al., 1996; Wintjens et al., 2001).

The upstream hydrophobic residues of the WW domain primarily include isoleucine, valine, phenylalanine, and/or tyrosine, whereas the downstream residues consist of arginine or lysine (Yaffe et al., 1997; Verdecia et al., 2000; Smet et al., 2005). The binding of the WW domain to pSer/Thr-Pro motifs is mainly maintained through hydrogen bonding and Van der Waals forces, with a binding dissociation constant at approximately 50 μm (Verdecia et al., 2000). The subcellular localization of Pin1 mainly depends on interactions between the WW domain and its corresponding substrates. *In vitro*, Pin1 primarily exists in the nucleus of cultured cells. However, in multiple cell types *in vivo*, Pin1 can be found in either the nucleus or cytoplasm, depending on the location of its substrates, which can be in either the nucleus or cytoplasm (Lu et al., 2002; Ayala et al., 2003; Liou et al., 2003).

The three-dimensional structure of a protein is determined by its AA sequence and folding patterns (Seckler and Jaenicke, 1992). During protein folding, the formation of disulfide bonds and the cis/trans isomerization of peptide bonds, especially those preceding proline residues, can influence protein modification (Warnke et al., 2014). Pro-directed protein kinases, including extracellular signal-regulated kinases (ERKs), c-Jun-N-terminal kinases (JNKs), p38 kinases, and Cyclin-dependent kinase 5 (CDK5), play significant roles in this process. While most peptide bonds are synthesized in the trans conformation, both cis and trans conformations are possible in peptidyl proline bonds because of the catalysis of peptide bond cis/trans isomerization by PPIases, including Pin1 (Matena et al., 2018).

Pin1 itself is subject to post-translational regulation (Lu et al., 2002; Lee et al., 2011; Rangasamy et al., 2012; Kim et al., 2015). The phosphorylation of Ser65 by polo-like kinase one increases the stability of Pin1 (Eckerdt et al., 2005). In contrast, small ubiquitin-like modifier (SUMO)-1 ubiquitinates Pin1, inhibiting its isomerase activity (Chen et al., 2013). Pin1 specifically catalyzes the isomerization of phosphorylated Ser/Thr-Pro motifs (Rostam et al., 2015). These cis/trans isomerization conformational changes result in stereoisomeric protein molecules with distinct structures and activities. These molecules then participate in the regulation of the activity, stability, phosphorylation level, and subcellular localization of target proteins, as well as interactions with other proteins (Yaffe et al., 1997). Consequently, Pin1 plays a pivotal role in regulating multiple biological processes. Pin1 also influences the activity of transcription factors such as β-catenin and NF-κB. It is involved in mitotic chromosome condensation through its interaction with topoisomerase (Topo) II alpha (Ryo et al., 2001; Ryo et al., 2002; Xu and Manley, 2007).

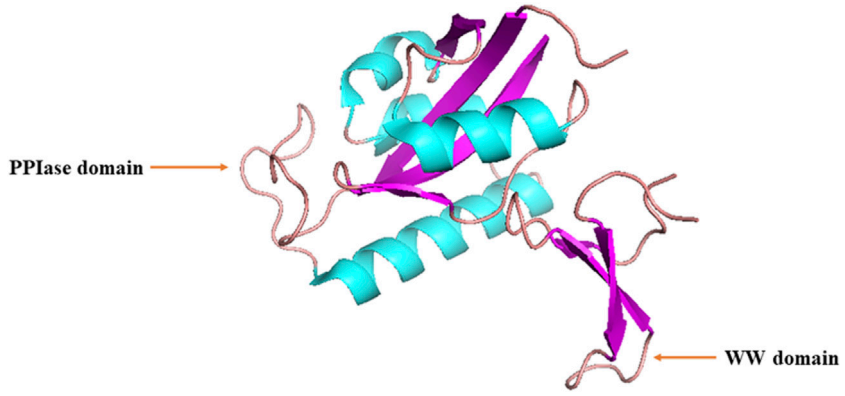

FIGURE 1
Structure of human Pin1 protein.

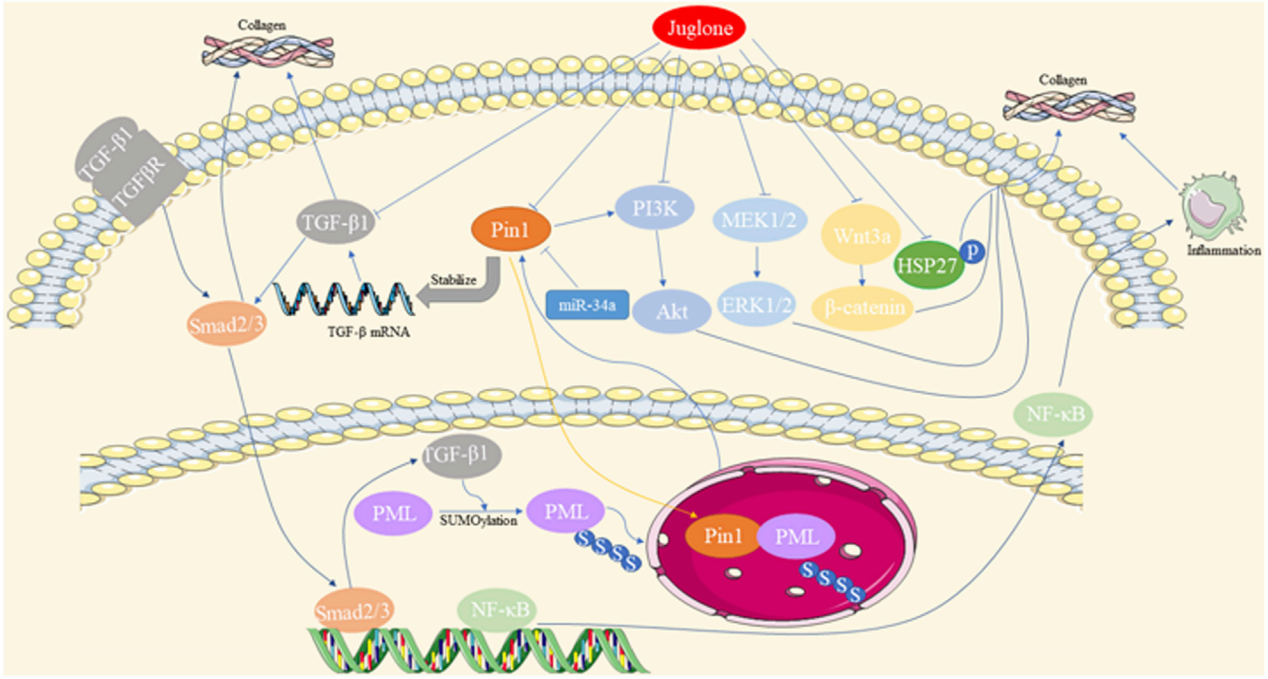

FIGURE 2
Mechanisms underlying the involvement of Pin1 in fibrosis.

3 Representative pathophysiological roles of Pin1

To date, most studies have focused on investigating the pathophysiological roles of Pin1 and its inhibitors in cancer, neurodegenerative diseases, and cardiovascular diseases. These diseases have similar pathological features. In this section, we summarize the molecular mechanisms of action of Pin1 in different tissues and cell types beyond the kidney under various pathological conditions. These insights may provide novel approaches for the treatment of kidney diseases.

3.1 Representative inhibitors of Pin1

Pin1 inhibitors are chemical or natural compounds that hinder Pin1 activity and/or expression. Compounds such as Epigallocatechin-3-gallate, Juglone, cyclic peptide 11, KPT-6656, compound 8, and PiB have been shown to inhibit Pin1 enzymatic activity *in vitro* (Hennig et al., 1998; Urusova et al., 2011; Guo et al., 2014; Bedewy et al., 2017; Campaner et al., 2017; Lv et al., 2018). API-1 reduces Pin1 expression levels (Pu et al., 2018). All-trans retinoic acid and arsenic trioxide suppress both Pin1 activity and expression (Wei et al., 2015; Kozono et al.,

2018). These Pin1 inhibitors are anticipated to offer therapeutic benefits to patients with a wide range of diseases.

3.2 Induction of fibrosis

Abnormal accumulation and deposition of extracellular matrix (ECM) proteins, as well as decreased expression and activation of matrix metalloproteinases (MMPs), contribute to fibrosis. Pin1 regulates the pathological process of fibrosis in multiple organs, including the heart, liver, and lungs. The mechanisms underlying the involvement of Pin1 in fibrosis are summarized in Figure 2.

Cardiac fibrosis is a common feature of end-stage heart diseases, such as diabetic cardiomyopathy (DCM), myocardial infarction (MI), and hypertrophic cardiomyopathy. Pin1, acting as a positive regulator of TGF-β1, colocalizes with promyelocytic leukemia protein (PML) and is involved in the TGF-β1/PML SUMOylation/Pin1 loop, all of which are upregulated in cardiac fibrosis (Liu et al., 2017; Wu et al., 2019). Pin1 inhibitors, such as Juglone, ginkgolic acid (inhibiting SUMO-1), miR-34a overexpression, and loureirin B, have been shown to alleviate cardiac fibrosis by reducing Pin1 expression and recruitment (Qiu et al., 2018; Zhang et al., 2021). Additionally, Juglone has been found to inhibit various signaling pathways, such as Pin1/TGF-β, TGF-β1/Smads, MEK1/2-ERK1/2, and α-SMA overproduction, in cardiac fibrosis induced by various heart diseases (Liu et al., 2016; Liu et al., 2017; Wu et al., 2018; Cheng et al., 2022). Juglone also disrupts the interaction between Pin1 and PML, destabilizing TGF-β mRNA and reducing p-Smad2/3 levels to protect against myocardial fibrosis (Wu et al., 2019).

Liver fibrosis is characterized by the excessive accumulation of ECM proteins, which can lead to hepatic cirrhosis and hepatoma development. Pin1 plays an essential role in fibrotic accumulation in liver pathologies such as non-alcoholic steatohepatitis (NASH). In clinical research, Pin1 has emerged as an independent predictor of liver fibrosis, with serum Pin1 levels being correlated with the histopathological stages of liver fibrosis in NASH (Cengiz et al., 2014). Additionally, genetic polymorphisms in PIN1 have been linked to the risk of hepatitis B virus-related liver cirrhosis among HBV-infected patients in Guangxi, China (Huang et al., 2018). Pin1 has been found to be upregulated in NASH mouse models and promotes liver fibrosis through various pathways (Nakatsu et al., 2012; Yang et al., 2014; Kim et al., 2016). Pin1 facilitates the association of Smad3 with WW domain-containing transcription regulators (TAZ). Pin1 downregulation, either through its inhibitors or siRNA, reduces the expression of collagen 1a1/2, α-SMA, and fibronectin, indicating its pivotal role in ECM component production in hepatic stellate cells (HSCs) and liver fibrosis (Aoyama et al., 2023). Moreover, Juglone suppresses liver fibrosis via the downregulation of the Wnt3a/β-catenin pathway in carbon tetrachloride-induced liver injury (Kim et al., 2016). Pin1 knockout (KO) mice are resistant to methionine choline-deficient (MCD) diet-induced NASH and fibrosis accumulation partially via the downregulation of peroxisome proliferator-activated receptor alpha (PPARα), as well as inhibition of NF-κB activation and its downstream inflammatory cytokines (Nozaki et al., 2009; Nakatsu et al., 2012). In dimethylnitrosamine (DMN)-induced mice livers, Juglone ameliorates liver fibrosis by reducing the expression of TGF-β1, α-SMA, and plasminogen activator inhibitor-I (PAI-1) through the downregulation of Erk-PI3K/Akt and p-Smad2/3 activation (Yang et al., 2014).

Pulmonary fibrosis is a chronic, progressive lung disease that can be triggered by various etiological factors, ultimately leading to the disruption of lung architecture. Studies have demonstrated that Pin1 plays a regulatory role in lung fibrosis, both in cases of acute lung injury and chronic asthma (Shen et al., 2008; Shen et al., 2012). According to Shen et al., Pin1 deficiency suppresses the expression of collagen I/III/V, PAI-1, and TGF-β1. This reduction in expression results in decreased interstitial pulmonary fibrosis owing to the accumulation of excessive cytoplasmic Smad6. This, in turn, leads to the reduction of TGF-β-induced p-Smad3 activation and its nucleus translocation, contributing to the mitigation of pulmonary fibrosis in acute bleomycin lung injury (Shen et al., 2012). Furthermore, the inhibition of Pin1 by Juglone has been shown to further reduce the expression of collagen I/III and stabilize TGF-β1 mRNA in pulmonary eosinophils. This action prevents airway fibrosis in a chronic asthma mouse model (Shen et al., 2008).

In conclusion, Pin1 regulates fibrosis in the heart, liver, and lungs by influencing ECM accumulation and molecular pathways. These findings highlight Pin1 as a potential target for fibrotic disease intervention.

3.3 Effects of oxidative stress

Oxidative stress arises from an imbalance between free radical production and antioxidant defenses, contributing to various diseases, such as diabetes, neurodegeneration, cardiovascular issues, and cancer (Sun et al., 2023). Pin1 has been shown to play a role in oxidative stress-related pathologies, as depicted in Figure 3.

Francesco et al. demonstrated that Pin1 exacerbates hyperglycemia-induced reactive oxygen species (ROS) production and mitochondrial oxidative stress in human aortic endothelial cells (HAECs) through the translocation of p66Shc, a prooxidant adaptor (Pinton et al., 2007; Paneni et al., 2015). Suppression of Pin1, through gene silencing, Juglone treatment, Vitamin D receptor (VDR) agonists, or bromocriptine-QR, alleviates chronic oxidative stress and vascular dysfunction induced by diabetes (Paneni et al., 2015; Costantino et al., 2016; Zhang et al., 2018; Cincotta et al., 2022). Similar effects of Pin1 on p66Shc translocation and ROS accumulation were observed in intestinal ischemia/reperfusion (I/R) injury and hippocampal neuronal oxidative stress (Zhu et al., 2014; Feng et al., 2017). Furthermore, Pin1 promotes mitochondrial oxidative stress in conditions such as ISO-induced cardiac fibrosis, alcoholic cardiomyopathy, and cardiomyocyte hypertrophy (Sakai et al., 2014; Wang et al., 2016; Wu et al., 2018). Fluvastatin mitigates endothelin-1-induced cardiomyocyte hypertrophy by suppressing Pin1 activity through the regulation of p-JNK and c-Jun (Park et al., 2012; Sakai et al., 2014). In contrast, Pin1 upregulates antioxidant response element-driven genes via the Kras/ERK/NRF2 axis in pancreatic cancer cells (Oke et al., 2020). Pin1 overexpression reduces ROS production and

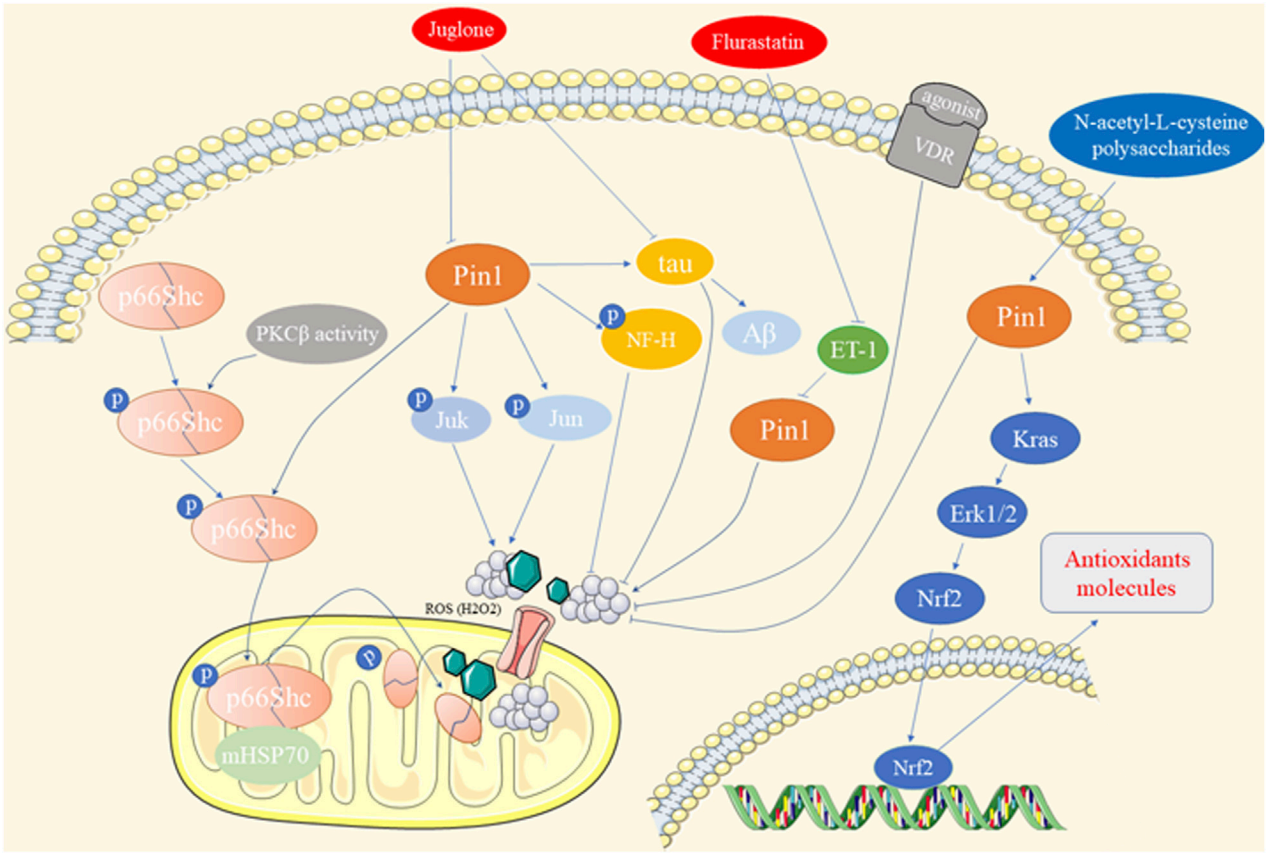

FIGURE 3
The role of Pin1 in oxidative stress-related pathology.

hepatic oxidative stress in arsenic- and CCl_4-induced hepatotoxicity (Zhang H. et al., 2022). N-acetyl-L-cysteine and polysaccharides from *Enteromorpha prolifera* restore Pin1 levels, reducing oxidative stress and protecting against hepatic injury (Guo et al., 2020; Zhang H. et al., 2022).

Oxidative stress induced by amyloid-β peptide (Aβ) plays a crucial role in AD in humans and animal models. Pin1 was found to colocalize with Tau, regulating its phosphorylation/dephosphorylation and inducing Aβ production (Robinson et al., 2011). Redox proteomic analyses revealed elevated levels of Pin1 in a mouse model of AD (Robinson et al., 2011). Juglone prevents Tau dephosphorylation at Thr-231, reducing oxidative stress in AD (Galas et al., 2006). Green tea catechins improve the AD phenotype by increasing Pin1 activity (Lim et al., 2013). Additionally, Pin1 enhances the phosphorylation of high-molecular-weight neurofilament protein (NF-H) through proline-directed kinases such as JNK3 in neurodegenerative disorders, including AD and amyotrophic lateral sclerosis (Rudrabhatla et al., 2008). However, some studies have reported lower Pin1 expression and activity, along with oxidative modifications, is associated with mild cognitive impairment, the hippocampus in AD, and adriamycin-induced cognitive dysfunction (Butterfield et al., 2006; Sultana et al., 2006; Joshi et al., 2010).

Given the varying effects of Pin1 on oxidative stress-related processes, its role in kidney disease is a compelling and significant area of research.

3.4 Effects of autophagy

Autophagy is a crucial process that maintains cellular homeostasis by breaking down damaged organelles, abnormal proteins, and pathogens within autophagosomes. These autophagosomes fuse with lysosomes for bulk degradation (Chao et al., 2022).

In the context of cadmium exposure, the expression of Pin1 shows interesting effects on autophagy. Previous investigation has shown that exposure of oral squamous cell carcinoma to cadmium (IC50 = 45 μM) decreases the expression of Pin1. Inhibiting Pin1 with siRNA results in suppressed autophagy, which is inversely associated with p-Akt and p-Ser-GSK3αβ levels (So et al., 2015). Similarly, Pin1 levels decrease following cadmium exposure in human hepatoma cells (HepG2) with an IC50 ≥ 6 μM, and the inhibition of Pin1 induces autophagy, likely through the upregulation of p-Ser-GSK3αβ (So and Oh, 2015). This Pin1-autophagy relationship has also been observed in senescent auditory hair cells, where Pin1 inhibition leads to LC3 upregulation and p62 downregulation (Lv et al., 2022). While changes in GSK3αβ expression levels have no impact on cadmium-induced Pin1 levels in HepG2, the inhibition of GSK-3β in mouse livers leads to Pin1 activation, suggesting that GSK-3β might mediate the role of Pin1 in autophagy (Zhang J. H. et al., 2022; Chao et al., 2022). Additionally, in tamoxifen-resistant breast cancer, elevated levels of Pin1 enhance its interaction with p-MEK1/2,

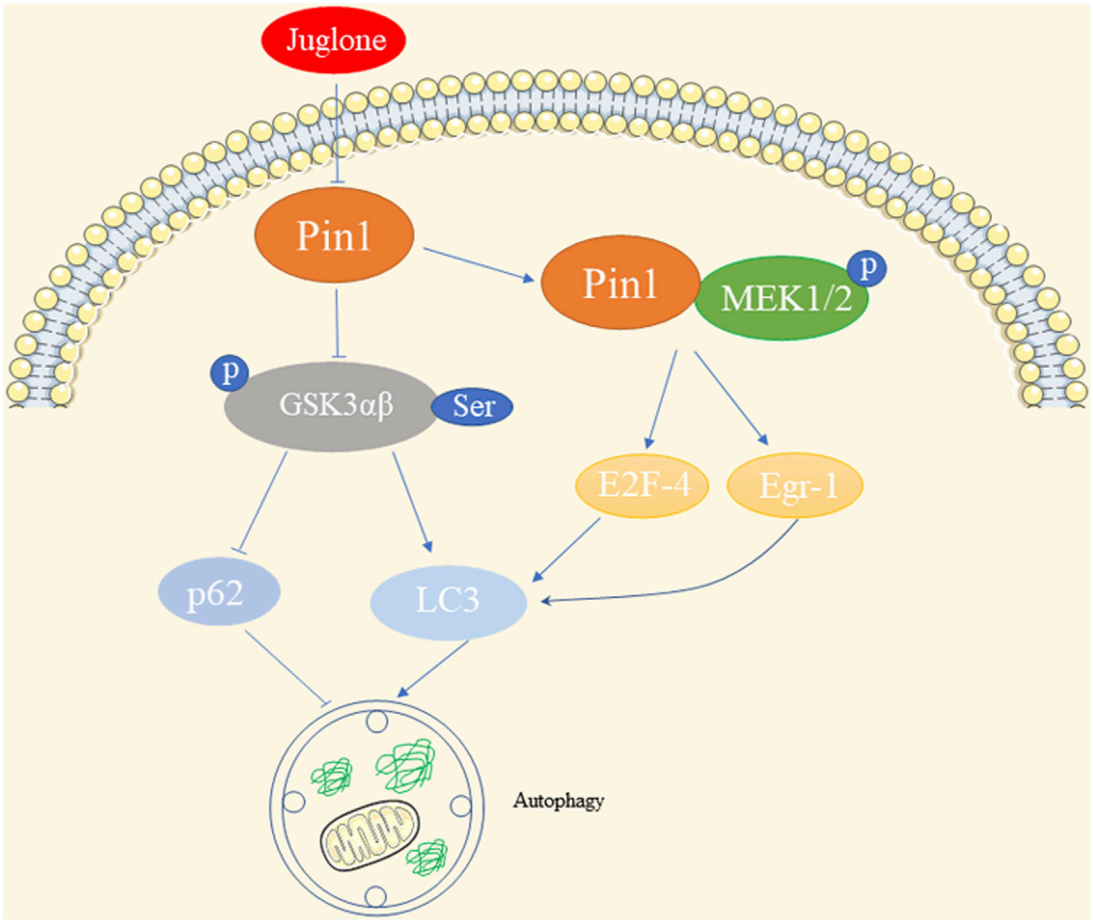

FIGURE 4
Effects of Pin1 on autophagy.

resulting in increased E2F-4- and Egr-1-driven LC-3 expression (Namgoong et al., 2010). This suggests a positive correlation between Pin1 levels and LC-3 expression, a representative indicator of autophagy, in estrogen receptor alpha-positive breast cancer.

In summary, cadmium exposure impacts Pin1 and subsequently influences autophagy through pathways involving p-Akt, GSK3αβ, and LC-3 in different cell types. The diverse effects of Pin1 on autophagy, as illustrated in Figure 4, justify the need for further exploration in various kidney diseases.

4 Effects of Pin1 on kidney disease

The role of Pin1 in mouse kidney development and kidney disease is of significant interest. Li et al. have highlighted the critical effects of Pin1 on embryonic mouse kidney development. They found that Pin1 is expressed in ureteric bud derivatives and mediates the function of protein kinase-X (PRKX), a regulator of epithelial morphogenesis, through the WW domain of Pin1 (Li et al., 2009). In contrast, Pin1 has been linked to the occurrence and progression of various kidney diseases (Thorpe et al., 2001; Hassan et al., 2022a; Patel et al., 2022). Genetic or pharmacological inhibition of Pin1 may help reduce renal injury by mitigating kidney fibrosis, oxidative stress, and apoptosis (Shen et al., 2016; Zhao et al., 2021). We have summarized the latest research findings and advancements regarding Pin1 in kidney disease in Figure 5 and Table 1.

4.1 Renal I/R injury

AKI is a heterogeneous condition characterized by a rapid decline in renal function over a short period (several hours to several days) and is typically accompanied by a sudden increase in serum creatinine and/or reduced urine output (Bellomo et al., 2012; Levey and James, 2017). Clinically, AKI is associated with high mortality and disability rates. The pathological processes underlying AKI can be summarized as follows: first, inadequate renal blood flow leads to cellular damage, apoptosis, and necrosis; second, inflammatory cell infiltration and a sustained inflammatory response play a crucial role in I/R injury and exacerbate kidney injury (Peng et al., 2023); and third, the accumulation of renal toxic substances, such as hemoglobin and myoglobin, leads to an overload of protein reabsorption in the kidneys, excessive production of reactive oxygen species (ROS), and even severe oxidative stress and endoplasmic reticulum (ER) stress. Currently, research on

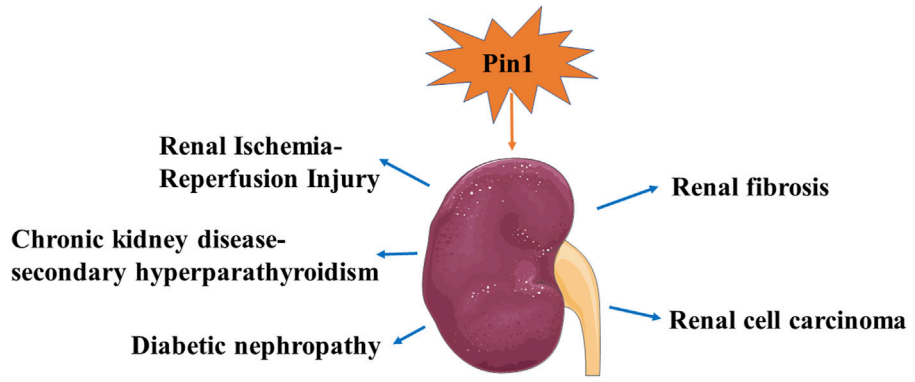

FIGURE 5
Recent research findings and advancements for Pin1 in kidney diseases.

Pin1 in AKI is limited to I/R kidney injury, and further studies are needed to explore its role in other types of AKI.

Renal I/R injury is a significant risk factor for AKI. Zhao et al. demonstrated that Pin1 inhibition, achieved either through Pin1 knockdown or Juglone treatment, alleviates structural and functional renal injury, increases SOD expression, and reduces the levels of MDA, ROS, and H_2O_2, which are indicators of oxidative stress. These effects are linked to decreased p38 MAPK expression in male Sprague-Dawley (SD) rats with I/R-induced AKI (Zhao et al., 2021). Furthermore, Yu et al. reported that Juglone or si-Pin1 protects against renal I/R-induced AKI by mitigating cellular damage and reducing the expression of ER stress markers, including GRP78, eIF2α, and CHOP. This protective effect is achieved by the downregulation of the Nrf-2/HO-1 pathway (Yu et al., 2022). Future studies should investigate the association between Pin1 and additional pathological processes triggered by I/R-related AKI as well as AKI resulting from sepsis or other nephrotoxic events.

4.2 Chronic kidney disease-secondary hyperparathyroidism (CKD-SHPT)

CKD is characterized by chronic structural and functional impairment of the kidneys lasting at least 3 months, resulting from various causes such as primary and secondary glomerulonephritis, tubular injury, and vascular lesions of the kidney (Lederer and Ouseph, 2007; Fraser, 2009). Pin1 is a crucial regulator of parathyroid hormone (PTH) stability (Kumar, 2009). In CKD, Pin1 isomerization becomes inactive, leading to reduced Pin1-mediated dephosphorylation and conformational changes of K-homology splicing regulatory protein (KSRP). Consequently, KSRP fails to effectively bind to PTH mRNA (Kilav-Levin et al., 2020; Hassan et al., 2022a; Hassan et al., 2022b). This results in decreased PTH mRNA destabilization by KSRP, whereas stabilization by adenosine-uridine-rich binding factor 1 (AUF1) increases, leading to elevated PTH mRNA levels and stability (Kilav-Levin et al., 2020) (Figure 6).

Furthermore, Morris et al. demonstrated in CKD rats and $Pin1^{-/-}$ mice that Pin1 inhibition reduces KSRP-PTH mRNA interactions, leading to increased serum PTH and PTH mRNA levels in CKD-SHPT (Nechama et al., 2009). Irena et al. also found that lower Pin1 expression levels are associated with nodular hyperplasia and influence PTH secretion in patients with end-stage renal disease (ESRD) (Tycova et al., 2016). Clinically, the PIN1 promoter polymorphism may be a significant genetic determinant in the etiopathogenesis of CKD-SHPT and may serve as a biomarker of susceptibility in the Chinese Han population and Indian patients with CKD (Zhao et al., 2017; Patel et al., 2022). Therefore, Pin1 plays a role in the pathogenesis of SHPT in patients with CKD. Pin1 inactivation in CKD affects PTH mRNA stability, and future research may uncover a broader role of Pin1 in CKD pathogenesis.

4.3 Diabetic nephropathy (DN)

DN is the most common cause of RF in patients with diabetes mellitus (DM) and often necessitates dialysis (Zhu et al., 2022). Worldwide in 2019, there were 2.62 million new cases, 134.58 million patients, 13.09 million disability-adjusted life years (DALYs), and 405.99 thousand deaths attributed to CKD-DM (Deng et al., 2021). Moreover, the incidence of DN in patients with DM is as high as 20%–50% (Dua et al., 2021). Type 2 diabetes is the most common type of diabetes and its pathological processes involve fibrotic deposition, oxidative stress, inflammation, apoptosis, and autophagy (Zhu et al., 2022).

Masa-Ki et al. demonstrated that Pin1 is involved in the protective effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors in the kidneys of mice with hyperglycemia induced by nicotinamide, streptozotocin, and a high-sucrose diet (NA/STZ/Suc). Canagliflozin normalizes elevated Pin1 expression levels, subsequently leading to a reduction in fibrosis and inflammatory cytokines (Inoue et al., 2019). Furthermore, high glucose (HG) increases the interaction between Pin1 and phosphorylated p66Shc in the mitochondria, resulting in increased oxidative stress and apoptosis in HK-2 cells. Reduction in Pin1 expression leads to decreased p66Shc activation and its translocation into the

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TABLE 1 Recent research findings and advancements for Pin1 in kidney diseases.

Kidney disease	Humans/Animals/ Cells	Treatments	Pin1 role in diagnostics or prognostics
Acute kidney injury (AKI)	I/R SD rats	Juglone or siPin1	-alleviate renal injuries in structure and function
	HK-2 cells		-increase SOD expression level
			-reduce expression levels of MDA, ROS and H_2O_2
			-reduce the expression levels of p38 MAPK
	I/R SD rats	Juglone or siPin1	-protect renal I/R injury from cellular damage
	HK-2 cells		-reduce expression levels of GRP78, elF2α and CHOP
			-down-regulate Nrf-2/HO-1 pathways
Chronic kidney disease-secondary hyperparathyroidism (CKD-SHPT)	CKD SD rats	Pin1 inhibition	-decrease KSRP-PTH mRNA interactions
	transfected cells		-increase serum PTH
	$Pin1^{-/-}$ mice		- increase PTH mRNA levels
	patients with ESRD	No treatment	-lower Pin1 expression levels
			-associate with nodular hyperplasia
			-influence PTH secretion
	Chinese Han patients with ESRD	No treatment	-PIN1 promoter polymorphism as vital genetic determinants in etiopathogenesis
			-Pin1 as biomarkers of susceptibility to CKD-SHPT
	Indian patients with ESRD	No treatment	-PIN1 promoter polymorphism as vital genetic determinants in etiopathogenesis
			-Pin1 as biomarkers of susceptibility to CKD-SHPT
Diabetic nephropathy (DN)	NA/STZ/Suc mice	Canagliflozin (SGLT2 inhibitors)	-normalize the upregulated Pin1 expression levels
			-decrease the fibrosis and inflammatory cytokines
	HK-2 cells	HG and siPin1	-reduce HG-induced p66Shc activation
			-reduce HG-induced p66Shc translocation into the mitochondrial compartment
Renal fibrosis	Mice with T2DM	HG	-Pin1 expression increased along with fibrosis of kidney
	mice with high phosphate	$Pin1^{-/-}$	-inhibit the ECM deposition and renal tubulointerstitial fibrosis through non-Smad pathways
	Lewis rats with UUO	Juglone	-decrease deposition of matrix, renal fibrosis, EMT, oxidative stress through p-Smad2 and p-HSP27 pathways
			-attenuate kidney fibrogenesis via Pin1-independent mechanisms
Renal cell carcinoma (RCC)	RCC	No treatment	-binding of Pin1 to TIS21 is reduced in the RCC
			-result in cell death
	mouse embryo fibroblasts	Pin1 deficiency	-lead to genomic instability
			-extensive tumorigenesis induced by the Ras oncogene
	human clear cell RCC tumors	Pin1 overexpression	-PIN1 gene is frequently deleted on chromosome 19p13.2 and under-expressed in human clear cell RCC tumors
	a xenograft tumor model		-Pin1 attenuates tumor growth through proliferation inhibition and apoptosis induction dependent on functional p53 in a xenograft tumor model
	nephroblastoma in a young C57BL/6 mouse	deletion of the Pin1 gene	-deletion of the Pin1 gene couples with Trp53 abnormality
	mice bearing 786-O cell-derived tumor	Pin1 inhibitor with PiB or Juglone	-suppress the PML protein ubiquitination and degradation
			-inactivated mTOR-HIF signaling pathway to enhance ccRCC suppression

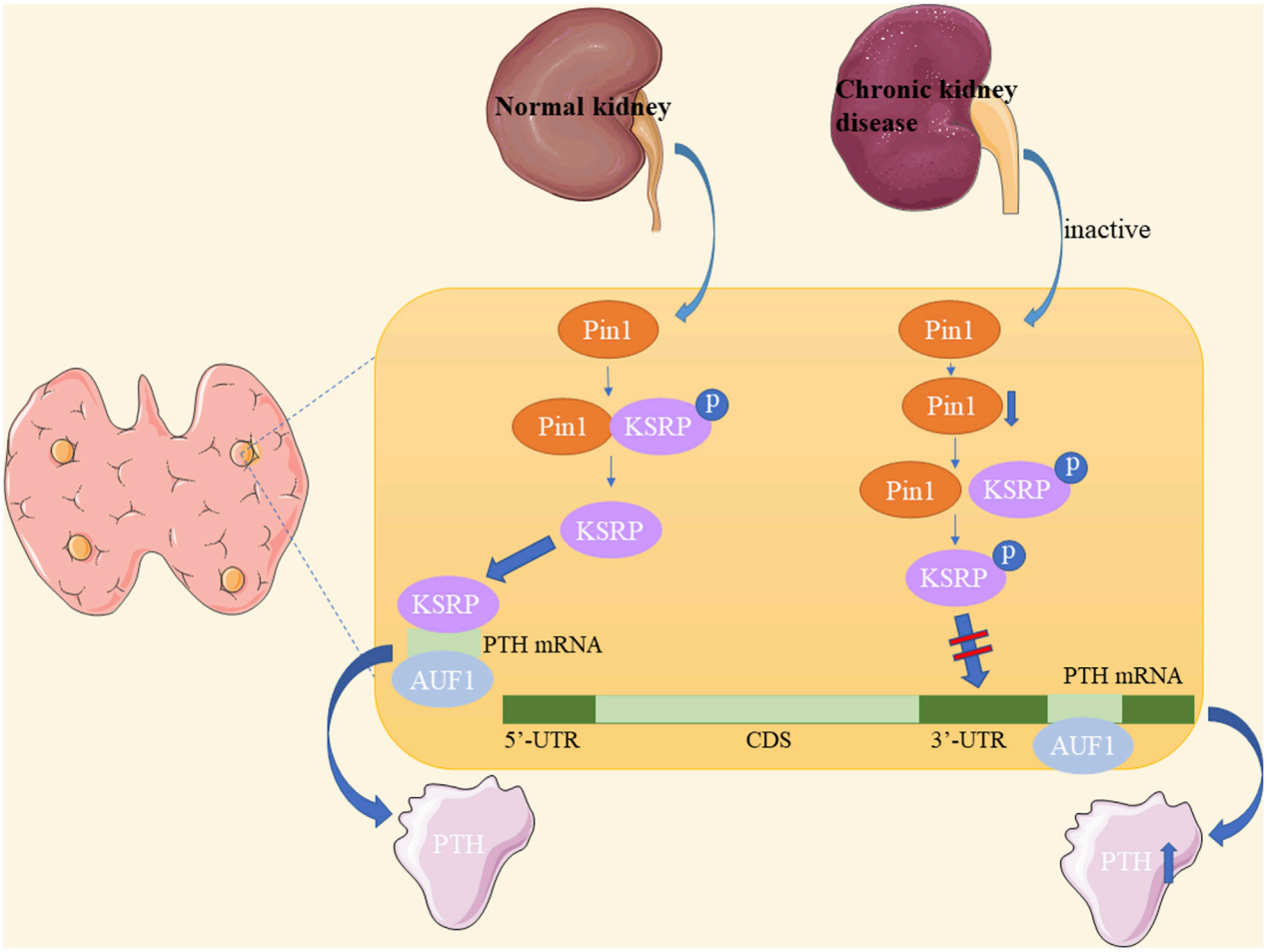

FIGURE 6
Underlying mechanisms of Pin1 in chronic kidney disease-secondary hyperparathyroidism (CKD-SHPT).

mitochondria in response to HG (Sun et al., 2010). These effects are also linked to increased HG-induced angiotensin II (Ang II) synthesis (Efrati et al., 2009; Sun et al., 2010).

4.4 Renal fibrosis

The maintenance of ECM homeostasis is crucial for renal function. Disruption of this balance, particularly in the epithelial-to-mesenchymal transition (EMT), is implicated in initiating and advancing renal fibrosis, especially in CKD (Liu, 2011; He et al., 2013). As mentioned earlier, Pin1 expression increases with kidney fibrosis in type 2 DM mice (Inoue et al., 2019). High phosphate levels, another risk factor for kidney fibrosis, exacerbate the decline in kidney function. Shen et al. discovered that Pin1 deficiency inhibits ECM deposition and renal tubulointerstitial fibrosis through non-Smad pathways in mice subjected to a high phosphate diet (HPD) (Shen et al., 2016). Juglone reduces matrix deposition, EMT, oxidative stress and attenuated renal fibrosis via the p-Smad2 and p-heat shock protein 27 (HSP27) pathways in Lewis rats with unilateral ureteral occlusion (UUO) (Reese et al., 2010). Pin1 regulates the pathological process of DN and exerts an antifibrotic effect during the deterioration of renal function under conditions related to high phosphate- and occlusion-induced kidney injury. Therefore, Pin1 plays a crucial role in maintaining ECM balance and preventing renal fibrosis.

4.5 Renal cell carcinoma (RCC)

RCC, also referred to as renal adenocarcinoma, is a malignancy arising from the urinary tubular epithelial system within the renal parenchyma (Linehan and Ricketts, 2019). RCC encompasses multiple subtypes originating from various segments of the urinary tubules, excluding tumors arising in the renal interstitium or pelvis (Wettersten et al., 2017).

Pin1 deficiency can lead to genomic instability and increased tumorigenesis. PIN1 is frequently deleted and under-expressed in human clear cell RCC tumors. The interaction between Pin1 and TIS21, a tumor suppressor that is highly expressed in normal proximal tubules of the kidney but is lost in RCC, leads to cell death. This suggests potential implications for Pin1 in RCC development (Struckmann et al., 2004; Lim et al., 2008). Previous studies have demonstrated that Pin1 deficiency can result in genomic

instability and extensive tumorigenesis when induced by the Ras oncogene in mouse embryo fibroblasts (Yeh et al., 2006). Brian et al. reported that the PIN1 gene is often deleted on chromosome 19p13.2 and is under-expressed in human clear cell RCC tumors. They found that Pin1 attenuates tumor growth by inhibiting proliferation and inducing apoptosis in a xenograft tumor model, which depends on functional p53 (Teng et al., 2011). Vittoria et al. reported the development of nephroblastoma in a young C57BL/6 mouse with a Pin1 deletion coupled with a Trp53 abnormality. This discovery provides novel insights into the relationship between Pin1 and nephroblastoma tumor pathogenesis (Castiglioni et al., 2013).

In contrast, the Pin1 inhibitors PiB and Juglone suppress the ubiquitination and degradation of promyelocytic leukemia (PML) proteins. Additionally, they inactivate the mTOR-HIF signaling pathway, leading to enhanced suppression of clear cell RCC in mice bearing tumors derived from 786-O cells (Lin et al., 2014). Therefore, Pin1 appears to play a significant role in the development of RCC.

5 Conclusion

Recently, multiple studies have highlighted the significant roles of Pin1 and its inhibitors in the pathophysiology of kidney diseases. Pin1 has been shown to contribute to pathological processes such as fibrosis, oxidative stress, and autophagy in various tissues and cell types, including the kidney. We present existing evidence for the involvement of Pin1 in conditions such as AKI, CKD-SHPT, DN, renal fibrosis, and RCC. However, the regulatory role of Pin1 in other kidney diseases remains unclear. These diseases include kidney transplantation and other forms of AKI such as sepsis, cisplatin nephrotoxicity, lupus nephritis, and IgA nephropathy. Furthermore, it is crucial to emphasize the need for both clinical and preclinical trials to elucidate the effects of Pin1 on kidney disease. In conclusion, Pin1 plays a vital role in the pathogenesis of kidney diseases, and modulating its expression (either upregulation or downregulation) may offer effective therapeutic strategies for various kidney disorders. In the future, regulating the expression of Pin1 is expected to be beneficial in the treatment of kidney diseases. For example, gene therapy may be used to modify Pin1 expression for treating kidney disease or inhibitors of Pin1 may be used to treat AKI and CKD. This opens new avenues for the early prevention and treatment of kidney disease.

Author contributions

SW: Writing–original draft. YZ: Writing–original draft. XT: Writing–original draft. SY: Writing–original draft. TC: Writing–original draft. JZ: Writing–original draft. XX: Writing–review and editing. FW: Writing–review and editing. WL: Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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