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REVIEW

Mechanisms of Macrophage Glycolytic Reprogramming and Interventional Effects of Traditional Chinese Medicine on Renal Fibrosis

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Abstract: Renal fibrosis (RF) is a common pathological outcome of multiple chronic kidney diseases (CKDs), accompanied by substantial extracellular matrix (ECM) deposition and gradual decline of renal function. To date, no clinically viable treatment can reverse progressive renal fibrosis, making it critical to uncover its pathogenic mechanisms. Macrophages display remarkable phenotypic heterogeneity in fibrotic kidneys. Dramatic metabolic reprogramming occurs in these immune cells, with elevated aerobic glycolysis serving as a dominant trait. This metabolic switch not only sustains the energy demand of activated macrophages but also promotes the formation of pro-inflammatory and pro-fibrotic phenotypes. Apart from glycolysis, dysregulated glutaminolysis and lipid metabolism also interact with glycolysis to aggravate renal damage. TCM, owing to its multi-component and multi-target advantages, has shown favorable preclinical effects against renal fibrosis. A growing body of evidence suggests that TCM-derived monomers, formulas, and extracts may exert anti-fibrotic actions by modulating macrophage glycolytic reprogramming. However, the field faces prominent challenges. All relevant data are limited to preclinical studies, with no clinical validation to date. Most research evaluates glycolytic activity indirectly via the expression of metabolic enzymes rather than direct metabolic flux measurement. Additionally, the pharmacokinetics, toxicity, and translational potential of TCM components remain inadequately characterized. This narrative review elaborates the molecular mechanisms of macrophage glycolytic reprogramming in renal fibrosis and summarizes preclinical research on TCM interventions, while clarifying current research deficiencies and future directions.

Keywords: macrophages, glycolytic reprogramming, renal fibrosis, traditional Chinese medicine, epigenetic modification

Introduction

Chronic kidney disease (CKD) is a global public health issue characterized by high morbidity, high disability, and high mortality. The global prevalence of CKD is approximately 13.4%, with more than 2 million deaths annually from related complications.[1–3] Renal fibrosis (RF) is a core pathological feature of CKD,[4,5] primarily manifested as activation of renal interstitial fibroblasts, excessive deposition of extracellular matrix, and destruction of renal tissue structure, ultimately leading to end-stage renal disease (ESRD).[5–7] Therefore, inhibiting or reversing renal fibrosis is critical for improving the prognosis of patients with CKD.[8]

Inflammation is a key driver of the development and progression of renal fibrosis.[9] As major effector cells of the innate immune system, macrophages consist of tissue-resident subsets and monocyte-derived infiltrating subsets.[10,11] Accumulating evidence from single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics has further revealed a spectrum of heterogeneous macrophage subsets including $TREM2^+$ and $SPP1^+$ cells in fibrotic kidneys.[12–14] For instance, via scRNA-seq analysis in a 5/6-nephrectomy rat model, Lu et al[13] verified that $CD206^+CD68^+$ M2 macrophages highly express the profibrotic genes TREM2 and IGF1, and can directly differentiate into fibrocytes, acting as a key profibrotic cell population.[13] Beyond macrophages, scRNA-seq has also revealed the heterogeneity of tubular epithelial cells during the transition from acute kidney injury (AKI) to chronic kidney disease (CKD). Li et al[15] reported that polyploid proximal tubular cells (>4N DNA content) arise after AKI and are predominantly enriched in pro-

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inflammatory and profibrotic cell clusters, with secreted phosphoprotein 1 (SPP1) acting as a pivotal hub gene.[15] Knockdown of SPP1 markedly alleviates renal fibrosis.[15]

In response to ischemia-reperfusion, toxins, or immune complex deposition, macrophages undergo phenotypic transformation tightly linked to fibrotic progression.[16–18] In recent years, metabolic reprogramming has been identified as a core hallmark of immune cell activation. Beyond glycolysis, dysregulated glutaminolysis, lipid metabolism and impaired mitochondrial function also participate in macrophage activities.[19,20] Glycolytic reprogramming remains the predominant metabolic pattern in activated macrophages.[21] Unlike quiescent macrophages that rely mainly on oxidative phosphorylation (OXPHOS) for energy supply, activated macrophages switch to aerobic glycolysis, namely the Warburg effect.[21–23] Notably, metabolic changes differ between acute injury and chronic lesions: metabolic shifts in acute kidney injury mostly serve adaptive tissue repair, while sustained pathological glycolysis dominates chronic renal fibrosis.[24]

Among the multiple metabolic pathways that regulate macrophage function, glycolysis has consistently been demonstrated as the most critical and upstream regulator of renal inflammation and fibrosis.[25] Glycolysis is the earliest and most consistent metabolic alteration during pro-inflammatory macrophage activation, operating upstream of multiple pro-fibrotic signaling cascades.[25,26] Lactate, the primary end product of glycolysis, not only serves as an energy substrate but also functions as a key signaling molecule that directly promotes fibroblast activation and extracellular matrix deposition.[27] While fatty acid oxidation primarily supports the survival of tissue-resident macrophages and M2-like polarization,[28] and glutaminolysis also contributes to the production of inflammatory cytokines,[29] these metabolic pathways play predominantly auxiliary and dependent regulatory roles and cannot independently drive sustained fibrotic progression. In contrast, glycolysis is more directly and broadly associated with pro-fibrotic macrophage phenotypes in the context of renal fibrosis.[30] Therefore, this review focuses on the well-characterized glycolytic pathway in macrophage-driven renal fibrosis, while acknowledging that other metabolic programs also participate in disease progression and warrant further in-depth investigation.

Current research on macrophage glycolytic reprogramming in renal fibrosis has achieved certain progress.[18,31] Studies have confirmed that aberrant activation of multiple signaling pathways, including HIF-1α, AMPK, mTOR, and PI3K/Akt regulates glycolytic metabolism and macrophage phenotypes, and further modulates inflammatory responses and fibrotic progression.[22,32–35] However, the precise molecular mechanisms by which macrophage glycolytic reprogramming drives renal fibrosis remain incompletely understood, and there is a lack of specific therapeutic agents in clinical practice.

Traditional Chinese medicine (TCM) has a long history in the treatment of kidney diseases, with its active components exerting multi-pathway and multi-target effects on RF.[36,37] Recent studies have revealed that TCM can modulate macrophage phenotypic polarization by targeting glycolytic reprogramming, thereby inhibiting renal inflammation and fibrosis.[38–41] Numerous in vitro and in vivo studies have demonstrated that TCM monomers and formulas can ameliorate renal fibrosis by inhibiting macrophage glycolytic reprogramming,[38,42] regulating macrophage polarization, and reducing the secretion of pro-inflammatory and pro-fibrotic factors.[43–47]

Nevertheless, existing relevant studies are relatively scattered, and the precise targets and molecular mechanisms of TCM remain to be further explored. This narrative review summarizes the roles and underlying mechanisms of macrophage glycolytic reprogramming in renal fibrosis, and outlines the research advances of TCM targeting this process. It aims to clarify the regulatory effects of TCM and provide new insights for mechanistic research and a theoretical basis for the translational study of TCM in renal fibrosis treatment.

Literature Search Strategy

Literature searches were conducted in PubMed and Web of Science from database inception to January 2026, with the language restricted to English. The search terms were constructed around the core themes as follows: ("macrophage" OR "macrophages" OR "macrophage polarization") AND ("glycolysis" OR "glycolytic reprogramming" OR "Warburg effect" OR "glucose metabolism") AND ("renal fibrosis" OR "kidney fibrosis" OR "renal interstitial fibrosis") AND ("traditional Chinese medicine" OR "TCM" OR "Chinese herbal medicine" OR "herbal extract" OR "herbal monomer"). The initial search yielded 250 relevant articles. After deduplication, 217 articles remained. Following title and abstract screening, 39 review articles, 7 bibliometric studies, and 39 articles with irrelevant research subjects were excluded, leaving 132 articles for full-text assessment. The literature screening process is illustrated in Figure 1, and the detailed search strategies are provided in Supplementary Material S1.

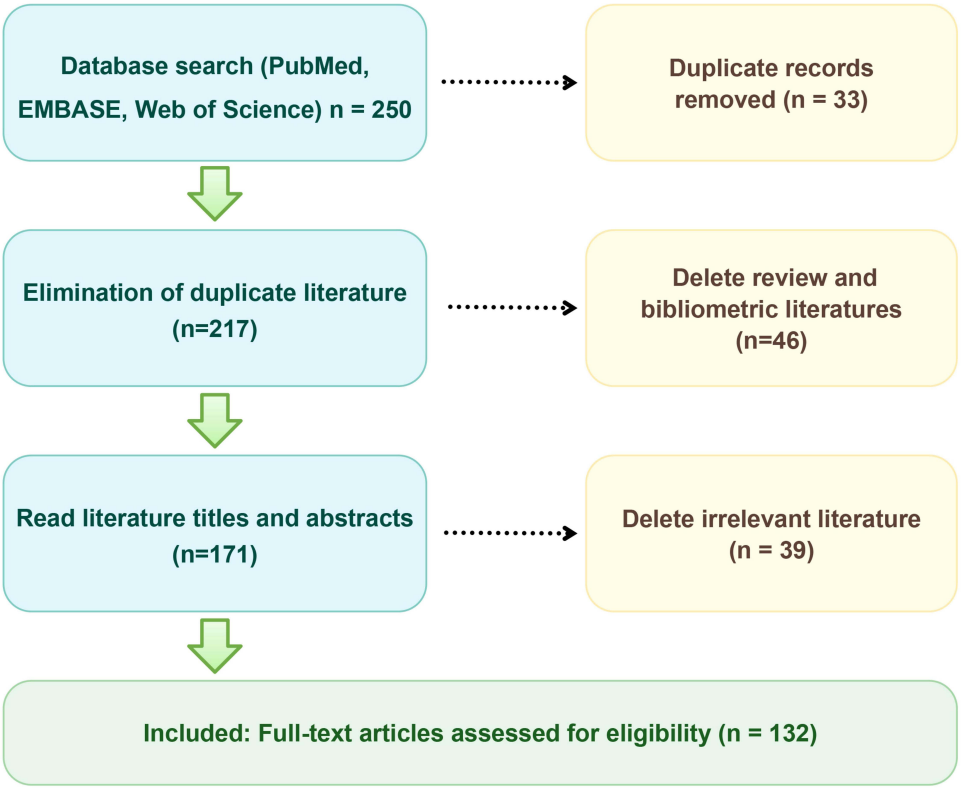

Figure 1 Literature screening flow diagram.

Macrophage Polarization and Its Role in Renal Fibrosis

Macrophage Phenotypic Polarization and Functional Plasticity

Macrophages are core effector cells of the innate immune system, exhibiting remarkable plasticity and heterogeneity. Their phenotype and function are precisely regulated by signals from the local microenvironment.[48] Based on activation status and functional characteristics, macrophages are broadly classified into two major subsets: classically activated (M1) and alternatively activated (M2) macrophages.[49–51]

M1 macrophages are induced by Th1-type stimuli such as lipopolysaccharide (LPS), interferon-γ (IFN-γ), or tumor necrosis factor-α (TNF-α). They highly express surface markers including inducible nitric oxide synthase (iNOS), CD86, and CD11c,[52] and secrete large amounts of pro-inflammatory cytokines (eg, TNF-α, IL-1β, IL-6) and chemokines, thereby contributing to pathogen clearance, antigen presentation, and pro-inflammatory responses. While moderate M1 activation supports host defense, excessive or persistent M1 polarization can lead to tissue damage and fibrosis.[17,53–55] M2 macrophages are induced by Th2-type cytokines such as IL-4, IL-13, IL-10, or transforming growth factor-β (TGF-β). They highly express markers including arginase-1 (Arg-1), CD206, and CD163, and secrete anti-inflammatory and pro-repair factors such as IL-10 and TGF-β, participating in tissue remodeling, angiogenesis, wound healing, and immune regulation. M2 macrophages can be further subdivided into M2a (pro-repair), M2b (immunomodulatory), M2c (anti-inflammatory), and M2d (pro-angiogenic) subtypes, reflecting their functional diversity.[17,55]

The Central Role of Macrophage Polarization Imbalance in Renal Fibrosis

Following kidney injury, macrophages are rapidly recruited to the site of damage, and their dynamic phenotypic changes are closely associated with disease progression.[56] In the early stage of acute kidney injury, infiltrating macrophages predominantly exhibit a pro-inflammatory M1 phenotype, participating in the clearance of necrotic cells and pathogens. As tissue repair progresses, macrophages gradually transition to an anti-inflammatory M2 phenotype, promoting tissue repair and restoration of homeostasis.[57,58] However, during the progression of chronic kidney disease, persistent injurious

stimuli lead to an imbalance in macrophage polarization, characterized by sustained accumulation of M1 macrophages or disruption of the M1/M2 switch, thereby driving the progression of renal fibrosis.[59–61]

Pro-fibrotic mechanisms of M1 macrophages: Overactivated M1 macrophages accelerate renal fibrosis through the following pathways: (1) secretion of pro-inflammatory cytokines such as TNF-α and IL-1β, which induce tubular epithelial cell apoptosis, injury, and epithelial-mesenchymal transition (EMT), thereby increasing the source of myofibroblasts;[17] (2) release of pro-fibrotic factors such as TGF-β1 and platelet-derived growth factor (PDGF), which directly activate renal interstitial fibroblasts, promote their transformation into myofibroblasts, and enhance extracellular matrix (ECM) synthesis;[17,62,63] (3) secretion of tissue inhibitors of metalloproteinases (TIMPs), which inhibit ECM degradation, leading to excessive ECM deposition.[32,64]

Dual roles and functional complexity of M2 macrophages: M2 macrophages exhibit significant spatiotemporal heterogeneity in their role in renal fibrosis.[17] During the repair phase, M2 macrophages exert anti-fibrotic and protective effects by secreting anti-inflammatory molecules such as IL-10 and Arg-1, while also promoting ECM degradation via matrix metalloproteinases (MMPs).[65,66] However, under persistent injurious stimulation, M2 macrophages may undergo functional transformation, acquiring a pro-fibrotic phenotype (termed M2-like pro-fibrotic macrophages), and contribute to myofibroblast activation and ECM deposition through the secretion of large amounts of TGF-β1, galectin-3, and other factors.[67,68] Notably, there is significant functional heterogeneity within M2 macrophages: the M2a subtype predominantly exhibits pro-fibrotic characteristics, whereas the M2c subtype primarily exerts anti-inflammatory and pro-repair functions.[56,69] Furthermore, recent advances in single-cell transcriptomics have revealed the presence of novel macrophage subsets in fibrotic kidney tissue, including TREM2+ lipid-associated macrophages, SPP1+ macrophages, and "cycling M2" macrophages. These subsets often co-express markers of both M1 and M2 phenotypes, exhibiting mixed phenotypic features.[70,71] These findings suggest that the simplistic binary classification of macrophages into M1 and M2 subtypes may be overly reductive, and that macrophages display a more complex continuous functional spectrum during the progression of fibrosis.

However, it is important to note that glycolysis is not inherently pathogenic. During acute kidney injury, transient glycolytic activation in macrophages supports rapid energy production for phagocytosis and bacterial clearance, representing an adaptive metabolic response that facilitates tissue repair.[72] It is only when injury becomes chronic and the metabolic shift persists—driven by sustained hypoxia, inflammation, and oxidative stress—that glycolytic reprogramming becomes maladaptive, promoting M1 polarization and fibrotic progression.[73] This distinction between adaptive (acute) and maladaptive (chronic) glycolytic remodeling is critical for understanding the context-dependent role of macrophage metabolism in renal fibrosis.

Strategies for Targeting Macrophage Polarization in the Treatment of Renal Fibrosis

Given the central role of macrophage polarization imbalance in driving renal fibrosis, modulating macrophage phenotypic switching and restoring the M1/M2 dynamic balance have emerged as promising therapeutic strategies for renal fibrosis. Current research primarily focuses on the following directions: (1) inhibiting M1 polarization or promoting M1-to-M2 conversion to alleviate inflammatory injury; (2) regulating the functional quality of M2 macrophages to prevent their transition toward a pro-fibrotic phenotype; and (3) targeting specific macrophage subsets (eg, CD206+, CD163+) and their metabolic features to achieve precise intervention.[23,59,74]

Although the above strategies have been validated in various animal models, clinical translation still faces challenges such as insufficient target specificity and low drug delivery efficiency. Notably, traditional Chinese medicine, leveraging its unique advantages of multi-component and multi-target characteristics, exhibits significant potential in modulating macrophage polarization. Through therapeutic principles such as "supporting healthy qi and eliminating pathogenic factors" and "promoting blood circulation and removing blood stasis", TCM can synergistically intervene in multiple signaling pathways, offering a promising avenue to overcome current bottlenecks in targeted therapy.[36,75]

Macrophage Glycolytic Reprogramming: A Key Driver of Renal Fibrosis

Features of Macrophage Glycolytic Reprogramming

Metabolic reprogramming refers to the remodeling of metabolic patterns that occurs in cells under pathological conditions to meet the demands of activation, proliferation, and functional adaptation.[76] Under resting conditions, macrophages primarily rely on mitochondrial oxidative phosphorylation (OXPHOS) for glucose metabolism, a process characterized by high energy efficiency that sustains cellular homeostasis.[21] Upon stimulation with pro-inflammatory signals such as lipopolysaccharide (LPS) and interferon-γ (IFN-γ), macrophages undergo a fundamental metabolic shift —even under aerobic conditions, glycolysis is markedly upregulated while oxidative phosphorylation is relatively suppressed. This phenomenon, termed glycolytic reprogramming or the Warburg effect, represents the core metabolic basis for macrophage involvement in the progression of renal fibrosis.[21,77]

The core features of macrophage glycolytic reprogramming can be summarized as follows: (1) Upregulation of key glycolytic enzymes. The expression of key enzymes, including hexokinase 2 (HK2), phosphofructokinase 1 (PFK1), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDHA), is significantly enhanced, driving the conversion of glucose to pyruvate and subsequently to lactate, thereby providing the metabolic foundation for macrophage activation in the renal injury microenvironment.[78] (2) Enhanced glucose uptake. Activated macrophages upregulate the expression of glucose transporters (GLUT1), leading to a marked increase in glucose uptake, which supplies sufficient substrate for the glycolytic pathway and ensures the metabolic demands of macrophages at local sites of renal injury.[79] (3) Adaptive switching of energy supply. Mitochondrial oxidative phosphorylation activity is suppressed, and the primary source of ATP generation shifts from OXPHOS to glycolysis. Although the ATP yield of glycolysis is lower than that of OXPHOS, its ability to rapidly generate energy meets the instantaneous high energy demands of activated macrophages, enabling their rapid participation in renal inflammation and fibrotic responses.[80] (4) Signaling regulatory functions of metabolic intermediates. Metabolic intermediates generated during glycolysis—such as pyruvate, lactate, and acetyl-CoA—not only serve as energy metabolites but also act as signaling molecules involved in the synthesis and regulation of inflammatory and effector cytokines, thereby reciprocally shaping the functional phenotype of macrophages.[81–84]

The synergistic effects of these metabolic features enable macrophages to rapidly activate, proliferate, and exert pro-inflammatory or pro-fibrotic functions within the renal injury microenvironment, thereby positioning them as key drivers of renal fibrosis progression.

Molecular Mechanisms of Macrophage Glycolytic Reprogramming in Driving Renal Fibrosis

Macrophage glycolytic reprogramming in renal fibrosis is controlled by an integrated network of signaling pathways that sense hypoxia, energy status, and inflammatory cues.[85] Rather than operating independently, these pathways form a highly interconnected regulatory circuit. Key components include upstream metabolic sensors (AMPK/mTOR), transcriptional hubs (HIF-1α and NF-κB), signal amplification nodes (PI3K/Akt), and metabolic-transcriptional feedback (STAT3).

Imbalance of the AMPK-mTOR Axis

In the chronically hypoxic and nutrient-deprived microenvironment of fibrotic kidneys, the balance between AMPK and mTOR determines the metabolic fate of macrophages.[86] AMPK activation suppresses anabolic processes and promotes oxidative phosphorylation, whereas mTOR activation drives glycolysis and M1 polarization—these two pathways function in mutual antagonism.[87] During the progression of renal fibrosis, chronic inflammation and local hypoxia lead to an imbalance in AMPK/mTOR signaling in macrophages.[88] Aberrant activation of mTOR upregulates the expression of key glycolytic enzymes such as HK2 and PFK1, enhances glycolytic flux, and induces polarization toward a pro-inflammatory M1 phenotype, promoting the secretion of pro-inflammatory and pro-fibrotic factors including TNF-α, IL-1β, IL-6, TGF-β1, and CTGF, thereby accelerating renal fibrosis.[89,90] Conversely, AMPK activation inhibits mTOR activity, reduces glycolysis, and promotes macrophage polarization toward an M2 phenotype.[91]

Notably, there is an mTOR-independent regulatory interaction between AMPK and HIF-1α.[92] AMPK can directly phosphorylate HIF-1α and promote its degradation via the ubiquitin-proteasome pathway.[92,93] During the repair phase of acute kidney injury, AMPK can limit excessive glycolysis through this mechanism, thereby protecting renal tissue.[93]

However, when injury progresses to the chronic stage, the renal microenvironment becomes increasingly hostile, characterized by persistent hypoxia, chronic inflammation, and oxidative stress.[94] Long-term overexpression of inflammatory factors (TNF-α, IL-1β) and sustained activation of the PI3K/Akt pathway cooperatively phosphorylate specific sites on the AMPKα subunit, preventing its upstream kinase LKB1 from activating AMPK via phosphorylation.[94,95] This ultimately results in sustained downregulation of AMPK phosphorylation and functional inactivation. The massive accumulation of HIF-1α induced by chronic hypoxia further transcriptionally inhibits AMPK-related regulatory proteins while relieving negative constraints on mTOR.[90,96] As a result, macrophage metabolism shifts irreversibly toward glycolysis, breaking phenotypic homeostasis and serving as a major driver of the transition to a pro-fibrotic macrophage phenotype.

Synergistic Activation of HIF-1α and NF-κB

HIF-1α is the core transcription factor linking the hypoxic microenvironment to macrophage glycolytic reprogramming.[97] In fibrotic kidneys, chronically reduced blood flow stabilizes HIF-1α in macrophages, which then binds to hypoxia-responsive elements (HREs) in the promoters of glycolytic genes (HK2, PKM2, LDHA), driving a glycolytic phenotype.[18,98,99] Simultaneously, HIF-1α upregulates the expression and secretion of TNF-α, IL-1β, and TGF-β1 in macrophages.[100] Pro-inflammatory cytokines amplify local inflammatory responses, while macrophage-derived TGF-β1 acts on renal interstitial fibroblasts, inducing their transformation into myofibroblasts and ultimately promoting excessive extracellular matrix (ECM) deposition.[101]

NF-κB, a core inflammatory transcription factor, exhibits bidirectional synergy with HIF-1α signaling.[102] On one hand, upon nuclear translocation, NF-κB directly binds to the promoter regions of pro-inflammatory cytokine genes, driving the transcriptional release of molecules such as TNF-α and IL-1β and amplifying the local inflammatory microenvironment.[103] On the other hand, NF-κB can bind to the HIF1A gene promoter to promote HIF-1α protein synthesis and inhibit prolyl hydroxylase (PHD) activity,[104] thereby reducing hydroxylation of HIF-1α at Pro564, blocking its ubiquitin-mediated degradation, and enhancing HIF-1α protein stability.[104,105] This indirectly increases the transcription of key glycolytic genes such as HK2, PFKFB3, and LDHA.[106] The aberrant glycolysis driven by HIF-1α leads to substantial intracellular lactate accumulation.[107] Lactate can translocate into the nucleus and catalyze histone lactylation. Histone lactylation remodels chromatin accessibility, preferentially enriching the promoter and enhancer regions of genes such as NFKB1, RELA, and other pro-inflammatory genes, thereby significantly upregulating the expression of NF-κB subunits and enhancing the nuclear retention time and transcriptional activity of the NF-κB complex.[24,102] Activated NF-κB in turn further activates HIF-1α, creating a vicious cycle of progressively amplified inflammatory dysregulation and metabolic disturbance in chronic kidney injury, continuously driving fibrosis progression.[108]

PI3K/Akt-Mediated Signal Convergence

PI3K/Akt serves as a core upstream hub that integrates extracellular inflammatory signals and distributes them to multiple downstream pathways, including HIF-1α, mTOR, and NF-κB, representing a key intersection linking inflammatory responses to macrophage glycolytic reprogramming.[109] In fibrotic kidneys, stimuli such as LPS and TNF-α significantly activate PI3K/Akt signaling in macrophages.[110] Phosphorylated Akt translocates into the nucleus, upregulates the transcription of HK2, PKM2, TNF-α, and IL-1β,[111,112] and inhibits PHD activity, thereby blocking hydroxylation of HIF-1α at Pro564 and amplifying the glycolytic transcriptional program.[112–114] At the same time, activated Akt phosphorylates and inhibits the TSC1/2 complex, relieving its inhibitory effect on mTOR. This means that PI3K/Akt can simultaneously initiate glycolytic regulatory pathways mediated by both HIF-1α and mTOR. PI3K/Akt also promotes IκB phosphorylation and degradation, accelerating NF-κB nuclear translocation and activating the NF-κB pathway upstream.[115,116]

Beyond these mechanisms, activated Akt upregulates the expression of CD11b integrin and CCR2 chemokine receptor through downstream transcription factors such as NF-κB and AP-1, promoting the recruitment of circulating monocytes to the injured renal interstitium and continuously amplifying local inflammatory cell aggregation.[117,118] Meanwhile, activated macrophages secrete paracrine factors such as TGF-β1 and FGF-2, inducing epithelial-mesenchymal transition (EMT) in renal tubular epithelial cells and activating fibroblasts, thereby forming a multicellular crosstalk network.[118–121] The PI3K/Akt pathway activates mTOR, which subsequently phosphorylates ULK1 and inhibits autophagy initiation,[122] leading to the accumulation of damaged organelles and toxic proteins and

exacerbating aberrant macrophage activation.[123] Additionally, this pathway participates in regulating macrophage pyroptosis and NLRP3 inflammasome activation, amplifying kidney inflammatory injury through programmed cell death.[113] This pathway also specifically regulates the phagocytic function and phenotype of $TREM2^{+}$ lipid-associated macrophages, potentially contributing to the transition from acute kidney injury to chronic fibrosis.[124]

STAT3 and PKM2 Nuclear Translocation

Persistently secreted cytokines such as IL-6 in the renal fibrotic microenvironment are the primary upstream signals activating STAT3.[125] Upon binding to its membrane receptor, IL-6 initiates an intracellular cascade, leading to STAT3 phosphorylation at Tyr705, followed by dimerization and nuclear translocation.[126] Activated STAT3 induces the nuclear translocation of cytosolic PKM2 and upregulates LDHA expression, thereby enhancing glycolytic flux and maintaining the pro-inflammatory phenotype of macrophages.[127,128] Activated PKM2 exhibits spatial functional differentiation: cytosolic PKM2 functions as a rate-limiting enzyme in glycolysis,[129] whereas nuclear-translocated PKM2 loses its classical metabolic function and becomes a transcriptional coactivator, assisting transcription factors in regulating target gene expression.[130] Unlike HIF-1α, which primarily drives initial glycolytic gene transcription, STAT3-mediated PKM2 nuclear translocation exerts a feedforward maintenance effect after the glycolytic program is established, preventing the reversal of the metabolic phenotype toward normal oxidative phosphorylation.[131]

At the transcriptional level, STAT3 and HIF-1α exhibit close synergistic interactions. In macrophages, STAT3 and HIF-1α can jointly bind to the promoter regions of target genes such as IL-1β, forming a transcriptional complex and synergistically enhancing transcription.[132] Moreover, lactate produced by glycolysis can influence STAT3 transcriptional activity by modulating its phosphorylation status.[133] Experimental evidence confirms that targeted intervention of STAT3 effectively inhibits PKM2 nuclear translocation, suppresses macrophage glycolysis, and alleviates renal fibrosis.[131]

Epigenetic Regulation by Metabolic Intermediates

In addition to the signaling pathways described above, glycolytic metabolites themselves participate in regulating macrophage function, forming a metabolite-driven epigenetic regulatory layer. These metabolites not only serve material and energy metabolism functions but also act as epigenetic modification substrates or signaling molecules, amplifying key steps in kidney injury and fibrosis.

Lactate, the end product of glycolysis, continuously accumulates in the chronically hypoxic microenvironment of the kidney.[134] Recent studies have revealed that lactate is not merely a metabolic waste product but directly regulates gene transcription through histone lactylation.[135,136] Specifically, lactate acts as a substrate for histone lactylation at H3K18la and H3K23la sites in macrophages.[136] This epigenetic modification relaxes chromatin and enriches the promoter regions of pro-inflammatory genes such as IL-6 and TNF-α, as well as glycolysis-related genes, potently activating gene transcription.[137]

Furthermore, succinate accumulates via the glutaminolysis pathway under hypoxic conditions.[138] It promotes ROS production through an SDH-dependent mechanism, activates inflammatory signaling, and cooperates with the NLRP3 inflammasome to promote macrophage pyroptosis, thereby amplifying inflammatory injury.[139] The AMPK/mTOR pathway can indirectly influence succinate levels by regulating glutamine metabolic flux.[140] Citrate is converted to acetyl-CoA by ATP-citrate lyase (ACLY), providing a substrate for histone acetylation and targeting M1 macrophage polarization markers, thereby promoting aberrant macrophage activation.[141] The accumulation of these metabolic intermediates demonstrates that metabolic remodeling is not merely a consequence of signaling pathway activation but also a driving force that further amplifies inflammatory and fibrotic signals.

Targeted Intervention of Traditional Chinese Medicine in Macrophage Glycolytic Reprogramming in Renal Fibrosis

Mounting evidence has established that aberrant macrophage glycolytic reprogramming drives persistent renal inflammation and fibrosis, making it a promising therapeutic target. Traditional Chinese medicine (TCM), with its multi-component and multi-target properties, has garnered attention for modulating immune metabolism. However, most current studies remain preliminary, with mechanistic links often inferred indirectly from glycolytic enzyme expression

rather than direct metabolic flux validation. This section critically summarizes TCM monomers, formulas, and extracts targeting macrophage glycolytic reprogramming in renal fibrosis. See Table 1 and Table 2.

TCM Monomers

Paeoniflorin

Paeoniflorin is a major active monoterpene glycoside extracted from *Paeonia lactiflora* and *Paeonia veitchii*, exhibiting a variety of pharmacological activities including anti-inflammatory, immunomodulatory, and antioxidant effects.[182,183] In recent years, multiple studies have revealed the multi-target mechanisms of paeoniflorin in renal fibrosis.[183] It has been reported that oral administration of paeoniflorin for 10 weeks significantly reduces urinary albumin excretion, ameliorates glomerular injury, and decreases $CD68^+$ macrophage infiltration in the kidneys of diabetic mice.[143] It restores M1/M2 macrophage balance by downregulating M1 markers (CD86, iNOS) and upregulating M2 markers (CD206, Arg-1).[143,184,185] In vitro experiments have further shown that paeoniflorin suppresses high glucose-induced M1 polarization of RAW264.7 macrophages and reduces the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, thereby alleviating inflammation and renal injury.[184,186]

In a high-glucose milieu, paeoniflorin inhibits the TLR2/4-MyD88-NF-κB pathway to reduce inflammatory cytokine production and macrophage accumulation. A TLR4 inhibitor recapitulates its anti-inflammatory effects, while TLR4 overexpression weakens its protection.[144,183,187] It directly binds the mechanosensitive ion channel Piezo1 to block Yoda1-triggered Ca^{2+} influx and HIF-1α-mediated endothelial-mesenchymal transition (EndMT). This process restores endothelial markers VE-cadherin and eNOS, and relieves microvascular loss and extracellular matrix deposition.[142] Notably, HIF-1α siRNA knockdown experiments and cellular thermal shift assays (CETSA) have confirmed that HIF-1α is a potential target for the anti-inflammatory action of paeoniflorin.[143,188,189] The Piezo1/HIF-1α axis bridges mechanotransduction and metabolism, supporting a role of paeoniflorin in regulating macrophage glycolytic reprogramming.

Despite these mechanistic insights, several limitations should be noted. First, the direct evidence linking paeoniflorin to macrophage glycolytic flux is still lacking; most conclusions are inferred from changes in glycolytic enzyme expression. Second, although HIF-1α has been identified as a target via siRNA and CETSA, the detailed binding mode and downstream metabolic consequences require further structural and functional validation. Third, the pharmacokinetic profile of paeoniflorin in renal tissue and its potential active metabolites remain underexplored.

Triptolide

Triptolide is a diterpenoid lactone compound extracted from *Tripterygium wilfordii* Hook. f. and is a major active component of this herb, exhibiting potent anti-inflammatory and immunosuppressive effects.[189–191] A series of studies have clarified the multi-target mechanisms of triptolide and its derivative (5R)-5-hydroxytriptolide (LLDT8) against renal fibrosis.[192,193] Triptolide activates the renal gluconeogenic pathway by upregulating the expression of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC1α) and phosphoenolpyruvate carboxykinase 1 (PCK1), thereby reducing lactate levels in renal tissue. Additionally, triptolide inhibits histone H3K18 lactylation modification, reducing pro-inflammatory cytokine expression and macrophage infiltration. The anti-fibrotic effects of triptolide can be reversed by a PCK1 inhibitor, suggesting that the PGC1α/PCK1 axis may represent an important pathway for its action.[145]

Triptolide also inhibits p38 mitogen-activated protein kinase (p38 MAPK) phosphorylation, thereby blocking NF-κB activation,[194] and downregulating the expression of pro-inflammatory cytokines such as TGF-β1, IL-1β, and TNF-α.[146,195] Notably, while suppressing TGF-β1 expression, triptolide concurrently reduces Smad2/3 phosphorylation and decreases the expression of fibronectin (FN) and collagens I and III, exerting anti-fibrotic effects.[196–198] Its derivative, (5R)-5-hydroxytriptolide (LLDT8), reduces the secretion of chemokines CCL2 and M-CSF1 from renal tubular epithelial cells, thereby disrupting the communication between tubular epithelial cells and macrophages, inhibiting macrophage activation and infiltration, and alleviating renal injury[192,193,199,200] The PGC1α/PCK1-mediated gluconeogenesis links glycolytic reprogramming to epigenetic regulation, providing new insights for renal fibrosis treatment. While the derivative LLDT8 exhibits an improved safety profile, long-term toxicity data remain insufficient, and caution is warranted when interpreting preclinical efficacy data without corresponding toxicological evaluation.

Table 1 Key Active Monomers from Traditional Chinese Medicine Targeting Macrophage Glycolytic Reprogramming to Ameliorate Renal Fibrosis

Name	Source Herb	Pharmacological Effects	Macrophage Regulatory Function	Glycolysis-Related Signaling Pathways	Key Measurements	Author (Year)
Paeoniflorin	*Paeonia lactiflora*, *Paeonia veitchii*	Anti-inflammatory, anti-oxidative stress	Inhibits M1 polarization, promotes M2 polarization; reduces macrophage infiltration	Inhibits HIF-1α; suppresses TLR2/4 signaling	ECAR; glucose consumption; lactate production; PKM2/LDHA expression	Li, R (2026);[142] Shi, C (2026);[143] Zhang, T (2017)[144]
Triptolide	*Tripterygium wilfordii*	Anti-inflammatory, immunosuppression	Inhibits M1 polarization; reduces macrophage infiltration	Promotes PGC1α/PCK1 axis to inhibit histone lactylation; inhibits MAPK/NF-κB pathway	Lactate level; H3K18 lactylation	Wang, Y (2026);[145] Zhu, B (2010)[146]
Berberine	*Coptis chinensis*, *Phellodendron amurense*	Hypoglycemic, hypolipidemic, anti-inflammatory	Inhibits M1 polarization, promotes M2 polarization	Inhibits IL-17A pathway; inhibits NF-κB/MAPK pathway; regulates AMPK/mTOR pathway	Seahorse ECAR; glucose uptake; lactate production; AMPK dependency verified	Fan, J.N (2026);[147] Tan, E (2023);[148] Rong, Q (2022);[149] Gong, S (2024)[43]
Curcumin	*Curcuma longa*	Anti-inflammatory, anti-oxidation	Inhibits M1 polarization; reduces macrophage infiltration	Activates Nrf2/Keap1/HO-1 pathway; inhibits TGF-β1/Smad pathway; inhibits NF-κB/MAPK pathway	Glucose uptake; lactate production; PKM2/HK2 expression	Soeikno, V (2013);[150] Hongtao, C (2018);[151] Melendez-Salcido, C. G (2025);[152] Chen, F (2021);[153] Zhou, X (2014)[154]
Hirudin	*Hirudo medicinalis*	Anticoagulation, anti-inflammatory	Inhibits M1 polarization; reduces macrophage infiltration (ED-1+, F4/80+); suppresses NLRP3 inflammasome	Inhibits mTOR/HIF-1α pathway; inhibits p38 MAPK/NF-κB pathway; regulates TGF-β1/Smad pathway	mTOR/HIF-1α pathway only (inferred); no glycolytic parameters measured	Long, C (2025);[155] Han, J (2020);[156] Lin, Q (2022);[157] Yang, K (2020)[158]
Catalpol	*Rehmannia glutinosa*	Anti-inflammatory, anti-apoptosis, endothelial protection	Inhibits M1 polarization, promotes M2 polarization; reduces macrophage infiltration	Inhibits RAGE/RhoA/ROCK pathway; inhibits Galectin-3/HIF-1α pathway; activates Nrf2/NF-κB pathway	RAGE/RhoA/ROCK pathway only (inferred); no glycolytic parameters measured	Shu, A (2021);[159] Sun, W (2023);[160] Liu, Z (2024)[161]
Quercetin	*Astragalus membranaceus*, *Sophora japonica*	Anti-oxidation, anti-inflammatory, hypoglycemic	Inhibits M1 polarization, promotes M2 polarization; reduces macrophage infiltration	Inhibits mTORC1/p70S6K pathway; inhibits Mincle-Syk/NF-κB pathway; inhibits NLRC5/NLRP3 pathway; activates SIRT1/PINK1 mitophagy	NF-κB, NLRP3 pathways; senolytic effects; no glycolytic parameters	Abudoureyimu, A (2025);[162] Lu, Q (2015);[163] Liu, T (2020)[164]
Myricetin	*Myrica rubra*	Anti-inflammatory, hypoglycemic	Promotes M2 polarization; reduces inflammatory cytokines	Activates PI3K/Akt pathway	PI3K/Akt pathway only (inferred); no glycolytic parameters measured	Xu, W (2024)[165]
Tectorigenin	*Pueraria lobata*	Improves glucose and lipid metabolism, anti-inflammatory	Inhibits M1 polarization; reduces macrophage infiltration	Activates AdipoR1/2-AMPK pathway	AdipoR1/2-AMPK pathway only (inferred); no glycolytic parameters measured	Yang, S (2020)[166]
Resveratrol	*Polygonum cuspidatum*	Anti-inflammatory, anti-oxidation	Inhibits M1 polarization; reduces macrophage infiltration	Activates AMPK/NOX4/ROS pathway; inhibits TGF-β1/Smad pathway	AMPK/SIRT1/NF-κB pathways only (inferred); no glycolytic parameters measured	Li, J (2010)[167]

Abbreviations: HIF-1α, hypoxia-inducible factor-1α; TLR2/4, Toll-like receptor 2/4; PGC1α, peroxisome proliferator-activated receptor gamma coactivator-1α; PCK1, phosphoenolpyruvate carboxykinase 1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; IL-17A, interleukin-17A; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; HO-1, heme oxygenase-1; TGF-β1, transforming growth factor-β1; Smad, mothers against decapentaplegic homolog; mTORC1, mammalian target of rapamycin complex 1; p70S6K, p70 S6 kinase; Mincle, macrophage-inducible C-type lectin; Syk, spleen tyrosine kinase; NLRC5, NLR family CARD domain containing 5; NLRP3, NLR family pyrin domain containing 3; SIRT1, sirtuin 1; PINK1, PTEN-induced putative kinase 1; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; AdipoR1/2, adiponectin receptor 1/2; NOX4, NADPH oxidase 4; ROS, reactive oxygen species.

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Table 2 Key Traditional Chinese Medicine Formulas Targeting Macrophage Glycolytic Reprogramming to Ameliorate Renal Fibrosis

Name	Herbal Composition	Pharmacological Effects	Glycolysis-Related Signaling Pathways	Macrophage Regulatory Function	Key Measurements	Author (Year)
Shenhua Tablet (SHT)	*Astragalus membranaceus*, *Salvia miltiorrhiza*, *Panax notoginseng*, etc.	Invigorates Qi, activates blood circulation, removes blood stasis	Inhibits HIF-1α/PKM2 pathway; inhibits PI3K/Akt pathway	Inhibits macrophage glycolysis; inhibits M1 polarization	Glucose uptake; lactate production; HK2/PKM2/LDHA expression; spatial metabolomics	Chen, Y (2025);[67] Li, R (2023);[168] Yuanchun, C (2025)[169]
Tangshen Formula (TSF)	*Astragalus membranaceus*, *Salvia miltiorrhiza*, *Rheum palmatum*, *Coptis chinensis*, etc.	Invigorates Qi, nourishes Yin, activates blood circulation	Activates SIRT1/NF-κB pathway	Inhibits macrophage infiltration; reduces MCP-1, IL-1β, TNF-α	SIRT1/NF-κB pathway only (inferred); no glycolytic parameters measured	Chen, P (2017);[170] Hu, L (2021);[171] Jiang Y (2026)[172]
Qihuang Jianpi Zishen Granules (QJZG)	*Astragalus membranaceus*, *Polygonatum sibiricum*, *Atractylodes macrocephala*, *Dioscorea opposita*, etc.	Invigorates Qi, strengthens spleen, nourishes kidney, consolidates essence	Activates AMPK/ULK1 pathway	Inhibits M1 polarization, promotes M2 polarization; inhibits macrophage glycolysis	Glucose uptake; HK2/GLUT1 expression; 2-DG positive control	Qian, A (2025)[40]
Yitangkang Decoction (YTK)	*Astragalus membranaceus*, *Dioscorea opposita*, *Salvia miltiorrhiza*, *Coptis chinensis*, etc.	Invigorates Qi, nourishes Yin, activates blood circulation, removes blood stasis, protects glomerular filtration barrier	Activates AMPKα1/ZDHHC8/SLC7A11/GPX4 axis; inhibits TGF-β/Smad pathway	Regulates M1/M2 macrophage polarization	AMPKα1/ZDHHC8/SLC7A11/GPX4 axis only (inferred); no glycolytic parameters measured	Yu, J (2026)[173]
Fufang Zhenzhu Tiaozhi Capsule (FTZ)	Margarita, *Salvia miltiorrhiza*, *Crataegus pinnatifida*, *Cassia obtusifolia*, etc.	Anti-inflammatory, hypolipidemic, hypoglycemic	Inhibits PI3K/Akt/NF-κB pathway	Promotes M2 polarization; reduces macrophage infiltration	PI3K/Akt/NF-κB pathway only (inferred); no glycolytic parameters measured	Li, M.H (2022);[174] Yang, Y. Q (2022)[175]
Shenkang Injection (SKI)	*Rheum palmatum*, *Salvia miltiorrhiza*, *Astragalus membranaceus*, *Carthamus tinctorius*, etc.	Invigorates Qi, activates blood circulation, removes turbidity	Inhibits IκB/NF-κB pathway; inhibits TGF-β/Smad3 pathway; activates Keap1/Nrf2 pathway; inhibits Wnt/β-catenin pathway	Reduces macrophage infiltration (CD68+, ED-1+)	NF-κB, Nrf2, Wnt/β-catenin pathways only (inferred); no glycolytic parameters measured	Wang, Y.N (2022);[176] Luo, L.P (2021);[45] Wei, H.T (2022);[177] Liu, Y (2023);[178] Xie, F (2023)[179]
Huangkui Capsule	*Abelmoschus manihot* (single herb)	Clears heat, removes dampness, resolves toxicity	Inhibits p38MAPK/HIF-1α pathway; inhibits Akt/mTORC1 pathway; inhibits TRPC6/Ca^{2+} pathway	Regulates M1/M2 macrophage polarization balance	p38MAPK/HIF-1α, Akt/mTORC1 pathways only (inferred); no glycolytic parameters measured	Liu, J (2025);[47] Gu, L.F (2020);[180] Mao, Z.M (2014)[181]

Abbreviations: HIF-1α, hypoxia-inducible factor-1α; PKM2, pyruvate kinase M2; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; SIRT1, sirtuin 1; NF-κB, nuclear factor-κB; MCP-1, monocyte chemoattractant protein-1; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; AMPK, AMP-activated protein kinase; ULK1, UNC-51-like kinase 1; ZDHHC8, zinc finger DHHC-type palmitoyltransferase 8; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; TGF-β, transforming growth factor-β; Smad, mothers against decapentaplegic homolog; IκB, inhibitor of κB; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; Wnt, wingless-related integration site; β-catenin, beta-catenin; p38MAPK, p38 mitogen-activated protein kinase; TRPC6, transient receptor potential cation channel subfamily C member 6.

Berberine

Berberine, an isoquinoline alkaloid from *Coptis chinensis* and *Phellodendron amurense*, exerts hypoglycemic, hypolipidemic and anti-inflammatory effects.[201,202] Similar to paeoniflorin, it downregulates CD86 and iNOS to restore M1/M2 macrophage balance, but modulates macrophage infiltration via the IL-17A pathway.[147] In a unilateral ureteral obstruction (UUO) mouse model, berberine was found to inhibit the NF-κB and MAPK signaling pathways,[203,204] reduce p-ERK phosphorylation, and downregulate the expression of inflammatory factors such as MCP-1, TNF-α, and IL-1β. Like triptolide, it inhibits Smad2/3 phosphorylation to slow fibrotic progression.[204]

In a high-glucose environment, berberine activates AMPK and inhibits mammalian target of rapamycin (mTOR) complex activity, forming an AMPK/mTOR regulatory axis, thereby promoting autophagy and alleviating pyroptosis and oxidative stress.[149,203] Further studies have demonstrated that berberine significantly downregulates the expression of key glycolytic enzymes, including hexokinase 2 (HK2), phosphofructokinase 1 (PFK1), and lactate dehydrogenase A (LDHA), in macrophages, suggesting reduced glycolytic activity.[43,149] An AMPK inhibitor partially reverses its activities, identifying AMPK as a candidate target. As a representative AMPK agonist, berberine provides an important basis for targeting macrophage glycolytic reprogramming in the treatment of diabetic kidney disease (DKD).

Berberine mainly functions through gut microbial metabolites rather than its parent form. Thus, in vitro results using micromolar concentrations cannot be directly applied to in vivo settings. Moreover, direct detection of glycolytic flux in berberine-treated macrophages is absent, and AMPK knockout models are needed to verify the AMPK dependency of its metabolic actions.

Curcumin

Curcumin is a natural polyphenolic compound extracted from the rhizome of *Curcuma longa*, exhibiting various pharmacological activities including antioxidant, anti-inflammatory, and anti-fibrotic effects. It is often used in combination with piperine to enhance bioavailability.[205–207] In a 5/6 nephrectomy-induced chronic renal failure rat model and a diabetic kidney disease mouse model, curcumin activates the Nrf2-Keap1 signaling pathway, promoting Nrf2 nuclear translocation, upregulating HO-1 expression, enhancing superoxide dismutase activity, and reducing malondialdehyde levels, thereby alleviating oxidative stress-induced renal injury and regulating macrophage metabolism.[110,150,208] Studies by Wang et al[110] have shown that curcumin inhibits the activation of the TLR4/NF-κB and PI3K/Akt signaling pathways in renal tissue of UUO mice,[110,209,210] reducing p-PI3K and p-Akt expression, decreasing the release of inflammatory cytokines such as IL-6, IL-1β, and TNF-α, while also inhibiting TGF-β1-induced epithelial-mesenchymal transition (EMT), downregulating α-SMA and vimentin expression, and upregulating E-cadherin expression.[110,207,208]

Curcumin exerts bidirectional control over PI3K/Akt depending on cell type and pathological conditions: it inhibits this pathway in renal fibrosis but activates it in adipocytes to facilitate glucose uptake.[110] By suppressing PI3K/Akt/HIF-1α, curcumin downregulates glycolytic enzymes (HK2, PFK1, PKM2) and reduces glucose uptake and lactate production.[211,212] It therefore inhibits macrophage glycolytic reprogramming and M1 polarization to alleviate diabetic renal fibrosis.[206]

Curcumin faces challenges for clinical translation due to poor oral bioavailability, rapid metabolism and extensive first-pass clearance. Piperine enhances its absorption, but it remains unclear whether curcumin can reach effective concentrations in renal macrophages in vivo. Most in vitro studies use supraphysiological concentrations (10–20 μM), so preclinical findings need careful interpretation. Though novel formulations optimize its pharmacokinetics, relevant research is still at an early stage.

Hirudin

Hirudin is a natural polypeptide component extracted from the salivary glands of the medicinal leech (*Hirudo medicinalis*). It exhibits multiple pharmacological activities, including anticoagulant, anti-inflammatory, and anti-fibrotic effects, and represents a characteristic component of animal-derived traditional Chinese medicine.[213] Recent studies have clarified its molecular mechanisms against renal fibrosis. In STZ-induced diabetic nephropathy rats, hirudin inhibits p38 MAPK/NF-κB activation, reduces TNF-α and IL-1β expression, and attenuates renal macrophage infiltration and podocyte apoptosis.[214] Furthermore, Long et al[155] discovered that hirudin reduces NLRP3 inflammasome activation by inhibiting the mTOR/HIF-1α signaling pathway,[155] and clears NLRP3 inflammasomes via the autophagy-lysosome

pathway,[215] thereby suppressing Caspase-1 cleavage and Gsdmd production. This subsequently inhibits the downstream STAT3/NLRP3 signaling pathway, alleviating pyroptosis and renal tubulointerstitial fibrosis.[216]

As a central regulatory hub for energy metabolism, mTOR is highly activated in M1 macrophages to sustain glycolysis.[112] Accordingly, hirudin-mediated mTOR/HIF-1α suppression implies its potential to reverse macrophage glycolytic reprogramming.[217] Hirudin A targets PIK3CA, AKT1 and mTOR to regulate the PI3K/Akt pathway, which closely interacts with glycolytic metabolism and cellular function.[218] Additionally, hirudin inhibits protease-activated receptor 1 (PAR1) expression through the S1P/S1PR2/S1PR3 signaling pathway, blocking TGF-β-induced epithelial-mesenchymal transition (EMT) and fibrosis in renal tubular epithelial cells.[157] As a unique animal-derived TCM monomer, hirudin provides novel insights for immune and metabolic regulation, while direct evidence verifying its regulatory effect on macrophage glycolysis remains lacking.

As a natural anticoagulant, hirudin carries inherent bleeding risks, restricting its application in advanced CKD patients with platelet dysfunction or combined antithrombotic treatment. Due to its polypeptide property, hirudin is only available via injection, resulting in poorer patient compliance than oral TCM agents. Furthermore, the in vitro effective concentrations (1–10 U/mL) adopted in most studies have not been validated to match achievable in vivo plasma levels.

Traditional Chinese Medicine Formulas

Shenhua Tablet (SHT)

Shenhua Tablet is a compound preparation composed of Chinese medicinal herbs including *Astragalus membranaceus, Salvia miltiorrhiza*, and *Panax notoginseng*. It exhibits the effects of benefiting qi, activating blood circulation, removing blood stasis, and dredging collaterals, and is clinically used for the treatment of chronic kidney disease and diabetic kidney disease.[219] In diabetic kidney disease models, 12-week treatment with Shenhua Tablet significantly reduced urinary protein excretion and the urinary albumin-to-creatinine ratio, demonstrating a clear renoprotective effect linked to targeting macrophage glycolytic reprogramming.[169,220]

Shenhua Tablet reduces $CD68^+$ macrophage infiltration in renal tissue and decreases the proportion of M1 macrophages. Metabolic assays showed that Shenhua Tablet reduced glucose uptake and lactate production in renal macrophages, accompanied by downregulation of HK2, PKM2, and LDHA.[169] PKM2, as a key rate-limiting enzyme of glycolysis, together with HIF-1α, constitutes an important signaling axis regulating macrophage metabolism.[221] By inhibiting this signaling axis, Shenhua Tablet may reduce glycolytic flux in macrophages, thereby modulating macrophage phenotypic polarization. Additionally, Shenhua Tablet exerts anti-fibrotic effects by inhibiting the PI3K/Akt pathway, as evidenced by reduced expression of fibronectin, α-SMA, and vimentin, thereby alleviating renal interstitial fibrosis.[115,168] Through network pharmacology analysis, Li et al[115] identified quercetin as the core anti-fibrotic active component of Shenhua Tablet and identified its primary target, AKT. Experimental evidence demonstrated that the anti-fibrotic effects of Shenhua Tablet could be reversed by the PI3K/Akt agonist 740Y-P.[115] These findings suggest that Shenhua Tablet may exert dual interventions on the HIF-1α/PKM2 and PI3K/Akt axes, synergistically inhibiting macrophage glycolytic reprogramming, blocking M1 polarization, and alleviating renal inflammation and ECM deposition.

As a multi-herb formula, Shenhua Tablet faces inherent challenges in standardization and reproducibility, including batch-to-batch variability in raw herb quality, extraction efficiency, and active component profiles. Although network pharmacology has identified quercetin and AKT as potential key targets, the relative contribution of each herb to macrophage glycolytic modulation remains to be dissected.

Tangshen Formula (TSF)

Tangshen Formula is composed of Chinese medicinal herbs including *Astragalus membranaceus, Salvia miltiorrhiza, Rheum palmatum*, and *Coptis chinensis*. It exhibits the effects of benefiting qi, nourishing yin, activating blood circulation, and dredging collaterals, and is clinically used for the treatment of diabetic kidney disease and its complications.[222] Multiple signaling pathways modulated by TSF are closely correlated with cellular glycolytic reprogramming. TSF activates sirtuin 1 (SIRT1) to deacetylate NF-κB p65 and block its nuclear translocation, thereby reducing the secretion of pro-inflammatory factors (TNF-α, IL-1β, IL-6, MCP-1), mitigating renal macrophage infiltration, and ameliorating glomerulosclerosis and tubulointerstitial fibrosis.[144,223]

Notably, SIRT1 is a metabolism-related deacetylase that directly interacts with PGC1α, deacetylating it to activate its transcriptional coactivator activity, thereby promoting mitochondrial biogenesis and fatty acid oxidation, ultimately reshaping cellular energy metabolism.[224] It also regulates FOXO-mediated metabolic homeostasis and drives macrophage polarization toward the anti-inflammatory M2 phenotype,[225] enabling TSF to reshape macrophage metabolic profiles indirectly.[224,226] Furthermore, Tangshen Formula promotes the activation of liver X receptor (LXR) and ATP-binding cassette transporter A1 (ABCA1), facilitating cholesterol efflux and reducing cholesterol deposition, thereby alleviating renal injury caused by lipid metabolism disorders.[227] Recent studies further reveal that Tangshen Formula inhibits the overexpression of soluble epoxide hydrolase (sEH), restoring insulin receptor substrate 2 (IRS2)-mediated PI3K/AKT signaling pathway activation, improving renal insulin sensitivity, while simultaneously inhibiting the p38 MAPK/NF-κB inflammatory pathway.[172] In a streptozotocin (STZ)-induced diabetic nephropathy rat model, Tangshen Formula significantly reduces TGF-β1 expression, inhibits extracellular matrix deposition, and alleviates renal interstitial fibrosis.[170,171]

Although the SIRT1-PGC1α and PI3K/AKT pathways are critical upstream regulators of glycolysis, no direct glycolytic detection has been performed in TSF-treated macrophages. The association between TSF and macrophage glycolytic reprogramming remains speculative and needs further validation. Methodologically, TSF suffers from batch-to-batch variations in herbal quality and extraction protocols. Moreover, the core active ingredients responsible for its metabolic and renoprotective effects have not been systematically characterized.

Qihuang Jianpi Zishen Granules (QJZG)

Qihuang Jianpi Zishen Granules are composed of Chinese medicinal herbs including *Astragalus membranaceus, Polygonatum sibiricum, Atractylodes macrocephala*, and *Dioscorea opposita*. It exhibits the effects of benefiting qi, strengthening the spleen, nourishing the kidney, and consolidating essence, and is clinically used for the treatment of chronic kidney disease and lupus nephritis.[228] In an MRL/lpr lupus mouse model, QJZG improved renal function, reduced 24-hour urinary protein, serum creatinine, and blood urea nitrogen levels, and alleviated renal tissue pathological damage by activating the AMPK/ULK1 signaling pathway.[40]

Metabolic assays revealed that treatment with QJZG significantly reduced glucose uptake in renal macrophages, accompanied by marked downregulation of the key glycolytic enzyme hexokinase 2 (HK2) and glucose transporter 1 (GLUT1).[40] Concurrently, the study employed the glycolytic inhibitor 2-deoxy-D-glucose (2-DG) as a positive control; 2-DG mimicked the metabolic regulatory effects of QJZG, further supporting that inhibition of glycolysis represents an important mechanism underlying its anti-inflammatory action.[40] By inhibiting macrophage glycolysis, QJZG subsequently modulates macrophage phenotypic polarization.[40] It also inhibits ERK/CREB phosphorylation via the GAS5/miR-21/Sprouty1 axis to suppress glomerular mesangial proliferation.[229] The inhibitory effect of the AMPK/ULK1 axis on mTOR/HIF-1α closely links glycolytic reprogramming with macrophage polarization regulation, and QJZG may intervene in macrophage metabolic reprogramming through this mechanism.

The AMPK/ULK1 axis, while implicated, should be further validated using AMPK knockout models. As a granule formulation, standardization of preparation across batches and the identification of active components responsible for the anti-fibrotic effects warrant further investigation.

Shenkang Injection (SKI)

Shenkang Injection is a compound preparation composed of Chinese medicinal herbs including *Rheum palmatum, Salvia miltiorrhiza, Astragalus membranaceus*, and *Carthamus tinctorius*. It exhibits the effects of benefiting qi, activating blood circulation, resolving stasis, and reducing turbidity, and is clinically used for the treatment of chronic kidney disease and diabetic kidney disease.[179] SKI exerts potent anti-inflammatory effects by downregulating TLR4, inhibiting the IκB/NF-κB cascade, reducing TNF-α and IL-1β levels, and decreasing renal macrophage infiltration to block inflammatory progression.[45] Since NF-κB upregulates key glycolytic enzymes, its inhibition may indirectly modulate macrophage glycolytic reprogramming.[230]

SKI also activates the Keap1/Nrf2 antioxidant pathway, facilitating Nrf2 nuclear translocation, upregulating HO-1 and SOD, and reducing MDA to relieve oxidative injury.[178,231] Nrf2 activation suppresses glycolytic enzymes PKM2 and LDHA, shifting cellular metabolism toward oxidative phosphorylation.[231] In inhibiting renal fibrosis, SKI acts

synergistically through multiple signaling pathways: it inhibits TGF-β1 expression, blocks Smad2/3 phosphorylation, and downregulates fibronectin (FN) and collagen I deposition;[232] inhibits Wnt expression and blocks β-catenin nuclear translocation, suppressing epithelial-mesenchymal transition (EMT) in renal tubular epithelial cells;[176,177] inhibits PDGFRβ expression, reducing pericyte-to-myofibroblast transformation and alleviating renal interstitial fibrosis;[233] and inhibits Smurf1/2 expression, reducing Smad7 ubiquitination and degradation, thereby enhancing the negative feedback regulation of Smad7.[233] As TGF-β1 induces glycolytic enzyme expression and myofibroblast activation,[234,235] SKI further inhibits the STING/TBK1/IRF3 pathway to reduce NK cell-mediated renal damage in UUO models.[236]

Importantly, pathways including NF-κB,[237] Nrf2,[238] and TGF-β/Smad[239] all exhibit direct cross-talk with macrophage glycolytic reprogramming. Therefore, the comprehensive regulation of these pathways by SKI suggests that it may exert renoprotective effects by intervening in macrophage glycolytic reprogramming; however, as an injectable formulation, SKI requires intravenous administration, which limits its applicability for long-term outpatient treatment compared to oral formulations. Quality control standards for injectable TCM preparations need to be rigorously maintained, and batch-to-batch consistency in active component profiles should be ensured.

Traditional Chinese Medicine Extracts

In addition to TCM monomers and formulas, TCM extracts also exert regulatory effects on macrophage glycolytic reprogramming in renal fibrosis. *Salvia miltiorrhiza* extract, rich in active components such as tanshinones and salvianolic acids, exhibits multi-target regulatory effects in renal fibrosis.[240] Cryptotanshinone, as one of the major active components of *Salvia miltiorrhiza*, exerts cardiorenal protective effects by inhibiting the PI3K/Akt/mTOR signaling pathway.[241,242] In a rat model of cardiorenal syndrome, oral administration of cryptotanshinone significantly improved cardiorenal function, reduced blood urea nitrogen, serum creatinine, and 24-hour urinary protein levels, and alleviated renal tissue pathological damage and fibrosis.[243] Further mechanistic studies indicated that cryptotanshinone significantly inhibited the phosphorylation levels of PI3K, Akt, and mTOR in renal tissue, while the protective effects were reversed by the PI3K activator 740Y-P,[243,244] suggesting that the PI3K/Akt/mTOR pathway may be a candidate target of its action. Accordingly, *Salvia miltiorrhiza* extract may alleviate renal interstitial fibrosis by inhibiting macrophage glycolytic reprogramming.

Astragalus membranaceus extract, rich in active components such as astragalus polysaccharides and astragaloside IV, exerts protective effects in renal fibrosis primarily by activating the AMPK signaling pathway.[245] Astragaloside IV enhances AMPK phosphorylation and suppresses mTOR, promoting autophagy to alleviate tubular injury and interstitial fibrosis.[246] AMPK activation also facilitates M2 macrophage polarization and increases anti-inflammatory IL-10 secretion.[246] This extract also ameliorates diabetic renal fibrosis via modulating the PI3K/Akt pathway.[247] Collectively, its active ingredients synergistically regulate macrophage glycolytic reprogramming through the AMPK/mTOR and PI3K/Akt pathways.

Furthermore, *Salvia miltiorrhiza* extract contains multiple active components (tanshinones, salvianolic acids), and the relative contribution of each to the observed anti-fibrotic effects remains unclear. Additionally, the oral bioavailability of astragaloside IV is low, raising questions about whether sufficient concentrations reach renal macrophages in vivo.

Conclusion

The overview diagram of the review is shown in Figure 2. Renal fibrosis represents the common final pathway for various chronic kidney diseases, with a complex pathogenesis involving multiple pathological processes including inflammatory responses, metabolic reprogramming, and extracellular matrix deposition.[32] Macrophages, as core effector cells of the renal innate immune system, exhibit activation and functional polarization that are highly dependent on metabolic reprogramming.[248] Under resting conditions, macrophages primarily rely on oxidative phosphorylation for energy production; however, within the renal injury microenvironment, macrophages undergo significant glycolytic reprogramming—prioritizing glycolysis even under aerobic conditions (the Warburg effect).[22] This metabolic shift not only provides energy and biosynthetic precursors for rapid cell activation but also reciprocally shapes the inflammatory phenotype of macrophages through the signaling functions of glycolytic intermediates such as lactate and pyruvate, driving their polarization toward a pro-inflammatory M1 phenotype.[22,248] Signaling pathways including HIF-1α, AMPK/mTOR, and PI3K/Akt constitute the core network regulating macrophage glycolytic reprogramming. Among these, HIF-

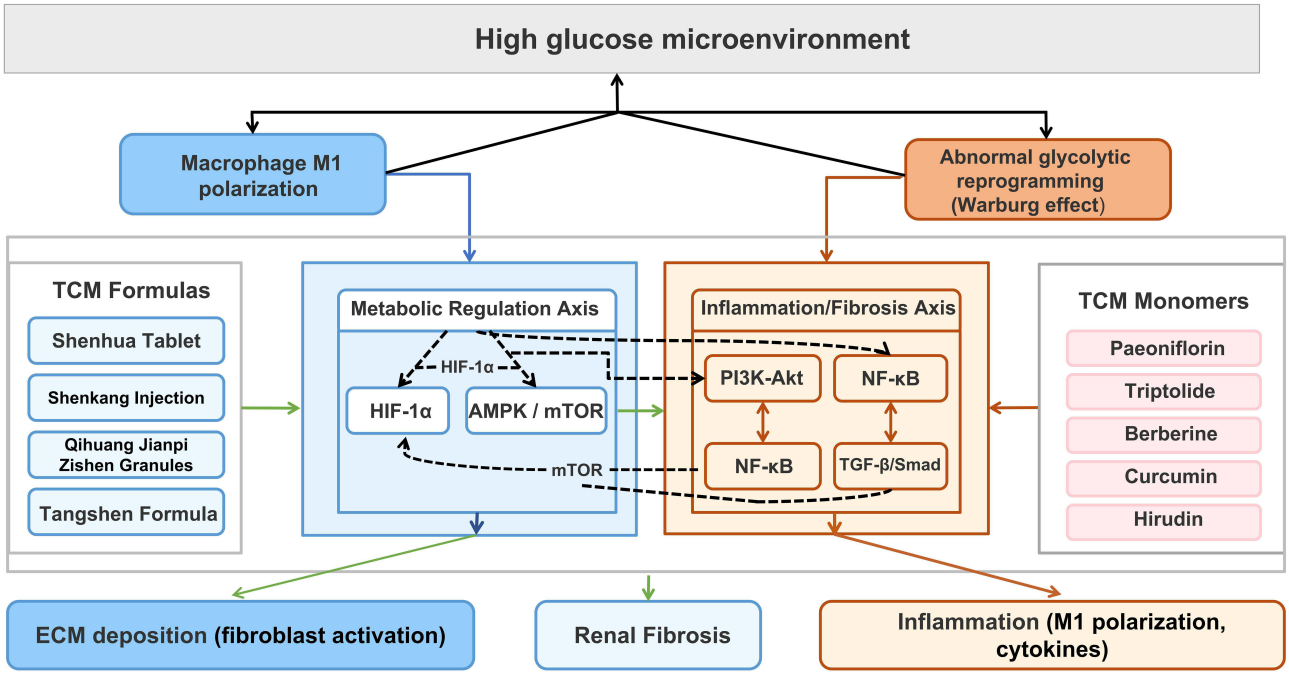

Figure 2 Mechanisms of Traditional Chinese Medicine in Targeting Macrophage Glycolytic Reprogramming to Ameliorate Renal Fibrosis.
Notes: In the hyperglycemic microenvironment, activation of HIF-1α, PI3K/Akt, p38MAPK, and AMPK/mTOR pathways drives macrophage glycolytic reprogramming, leading to M1 polarization and inflammatory responses. As illustrated, TCM monomers and formulas (*Paeoniflorin, Triptolide, Berberine, Curcumin, Hirudin, Shenhua Tablet, Tangshen Formula, Qihuang Jianpi Zishen Granules*) target these pathways to inhibit glycolytic reprogramming, suppress M1 polarization, and alleviate renal fibrosis. Arrow colors indicate: green, TCM-mediated inhibition; blue, M1 macrophage-driven pathological cascade; orange, glycolysis-driven pathological signaling; black dotted lines, bidirectional crosstalk/feedback between metabolic and inflammatory axes.

1α acts as a sensor of the hypoxic microenvironment, directly regulating the expression of key glycolytic enzymes;[32] AMPK/mTOR functions as an energy sensor, balancing anabolic and catabolic metabolism; and PI3K/Akt serves as an integrator of inflammatory signals, linking exogenous stimuli to metabolic reprogramming.[249]

Traditional Chinese medicine (TCM), leveraging its unique advantages of multi-component and multi-target characteristics, can inhibit macrophage glycolytic reprogramming, modulate macrophage phenotypic polarization, and reduce the secretion of pro-inflammatory and pro-fibrotic factors by targeting the aforementioned signaling pathways, thereby ameliorating renal fibrosis.[250,251] Both TCM monomers and compound formulas exert anti-fibrotic functions through distinct but synergistic metabolic regulatory mechanisms. Among them, Shenhua Tablet and Qihuang Jianpi Zishen Granules have been reported to modulate macrophage glycolytic metabolism, providing novel mechanistic clues for TCM intervention in renal fibrosis.[40,168]

Nevertheless, several translational and mechanistic limitations must be acknowledged. First, existing evidence is predominantly preclinical; large-scale, multicenter clinical trials are lacking. Second, the multi-component synergistic mechanisms of TCM formulas remain ambiguous, with insufficient data on renal targeting, metabolic transformation, and effective dosing. Third, batch-to-batch and geographical variations in herbal materials undermine reproducibility. Fourth, most studies rely on glycolytic enzyme expression rather than direct metabolic flux detection. Additionally, potent components such as triptolide exhibit toxicity concerns, and dose-effect and safety data remain inadequate.

Future research should precisely address the aforementioned mechanistic ambiguities and translational bottlenecks. Clinically, rigorous prospective randomized controlled trials incorporating metabolic biomarkers (eg, lactate, MCP-1, TGF-β1) are essential to validate the clinical efficacy of TCM in modulating macrophage glycolytic reprogramming. Mechanistically, benefiting from emerging single-cell and spatial omics technologies that have previously defined renal pro-fibrotic macrophage subsets, further application of these tools is warranted to resolve macrophage heterogeneity-related controversies.[249] Integrating lipid metabolomics with glycolytic flux analysis will provide a more comprehensive understanding of macrophage metabolic reprogramming in renal fibrosis. Specifically, scRNA-seq studies have identified

TREM2$^+$ macrophages as a key pro-fibrotic population driving renal fibrotic progression,[13] while SPP1 has been recognized as a core hub gene mediating AKI-to-CKD transition in renal macrophages.[15] Integrating these findings, future omics studies can precisely dissect whether TCM exerts subset-specific regulation and selectively targets pro-fibrotic macrophage subpopulations. Moreover, direct metabolic flux analysis, including Seahorse extracellular flux detection and stable isotope tracing, is urgently required to accurately quantify glycolytic activity and verify TCM-mediated metabolic remodeling, rather than relying solely on glycolytic enzyme expression.[252] To improve therapeutic specificity, cell-specific targeting strategies, such as macrophage-specific nanoparticle delivery and cell-type-specific promoter systems,[248] should be developed to achieve precise renal macrophage intervention without disturbing normal renal cell metabolism. Additionally, the role of epigenetic modifications such as histone lactylation mediated by glycolytic intermediates (eg, lactate) in macrophage polarization warrants in-depth investigation to explore novel mechanisms by which TCM regulates immune cell function through the metabolism-epigenetics axis.

Abbreviations

Akt, protein kinase B; AMPK, AMP-activated protein kinase; Arg-1, arginase-1; CKD, chronic kidney disease; CRF, chronic renal failure; DKD, diabetic kidney disease; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transition; FN, fibronectin; FTZ, Fufang Zhenzhu Tiaozhi capsule; GSDMD, gasdermin D; HIF-1α, hypoxia-inducible factor-1α; HK2, hexokinase 2; HO-1, heme oxygenase-1; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-10, interleukin-10; iNOS, inducible nitric oxide synthase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; PI3K, phosphatidylinositol 3-kinase; PKM2, pyruvate kinase M2; QJZG, Qihuang Jianpi Zishen Granules; SKI, Shenkang Injection; SHT, Shenhua Tablet; STAT3, signal transducer and activator of transcription 3; STZ, streptozotocin; TGF-β1, transforming growth factor-β1; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; TSF, Tangshen Formula; UUO, unilateral ureteral obstruction.

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Schematic diagrams were created using BioRender (https://biorender.com/).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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