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Roxadustat beyond anemia: A review of its pleiotropic mechanisms and translational potential

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ABSTRACT

Roxadustat, a first-in-class oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), has been approved for the clinical management of anemia secondary to chronic kidney disease (CKD). Previously published reviews generally focus on single-organ or individual disease manifestations, and a comprehensive systematic overview regarding its potential indications across multiple organ systems remains lacking. Beyond stimulating erythropoiesis, roxadustat triggers extensive transcriptional cascades via systemic stabilization of hypoxia-inducible factor (HIF), thereby exerting pleiotropic pharmacological actions throughout diverse organs. Accumulating preclinical findings and emerging clinical data verify that roxadustat facilitates cardiovascular injury repair, confers neuroprotection, remodels systemic metabolism, maintains iron homeostasis and modulates the tumor microenvironment, conferring promising translational prospects for repurposing in various non-anemic disorders. Nevertheless, widespread activation of the HIF signaling pathway is accompanied by safety concerns including tumor progression promotion, adverse vascular events and endocrine dysfunctions. From a multisystem perspective, this review systematically integrates the molecular mechanisms, preclinical outcomes and translational evidence of roxadustat to fill the existing gaps in available literature. We further highlight that precise patient stratification and standardized long-term safety surveillance are indispensable to fully exploit the therapeutic potential of roxadustat beyond anemia treatment.

Keywords: *Roxadustat, HIF-PHI, HIF-α stabilization, CKD-associated anemia and drug repurposing*

INTRODUCTION

Anemia is a frequent and debilitating complication of CKD, contributing significantly to cardiovascular morbidity, reduced quality of life, and increased mortality (Li & Lindholm, 2022). The cornerstone of management has historically been therapy with injectable erythropoiesis-stimulating agents (ESAs), which directly supplement erythropoietin levels. However, the efficacy of ESAs can be constrained by challenges such as parenteral administration, hyporesponsiveness, particularly in the presence of inflammation and concerns regarding potential adverse cardiovascular events (Drüeke & Massy, 2019). Crucially, ESAs do not address the dysregulated iron homeostasis, often characterized by elevated hepcidin, which leads to functional iron deficiency and further blunts the hematopoietic response (McDonnell & Kalra, 2025).

The development of orally administered hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) marks a fundamental advancement in anemia therapy, with Roxadustat being a first-in-class agent in this category (Dhillon, 2019). Rather than directly supplying exogenous hormones, Roxadustat leverages the body's own adaptive mechanisms to hypoxia. Its mechanism of action involves the stabilization of HIF-α subunits, which act as master transcription factors. This leads to the coordinated transcriptional upregulation of a suite of hypoxia-responsive genes, most notably endogenous erythropoietin (EPO) (Yang et al., 2021). This approach not only stimulates erythropoiesis but also, critically,

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improves iron availability and utilization by downregulating hepcidin, thereby overcoming the iron sequestration common in CKD (Li et al., 2020).

While the efficacy of Roxadustat in the management of renal anemia is well-established, its therapeutic action via the systemic activation of the HIF pathway suggests a far broader clinical potential. The pleiotropic effects governed by HIF signaling extend well beyond hematopoiesis to include critical processes such as angiogenesis via Vascular Endothelial Growth Factor (VEGF), cellular energy metabolism through Glucose Transporter 1 (GLUT-1), and modulation of inflammation and cellular stress responses (Dhillon, 2019). Given this multifaceted biological activity, investigating the repurposing of Roxadustat for non-hematologic conditions is a compelling and largely underexplored research frontier.

Molecular mechanisms underpinning non-anemic effects

HIF stabilization and downstream pathways

The pleiotropic effects of Roxadustat are rooted in its ability to pharmacologically activate the HIF signaling pathway, the principal cellular system for adapting to low oxygen availability. HIF is a heterodimeric transcription factor composed of a constitutively expressed HIF-1β subunit and an oxygen-labile α-subunit (HIF-1α, HIF-2α, or HIF-3α) (Yang et al., 2021). The activity of this pathway is tightly regulated by post-translational modifications of the HIF-α subunit.

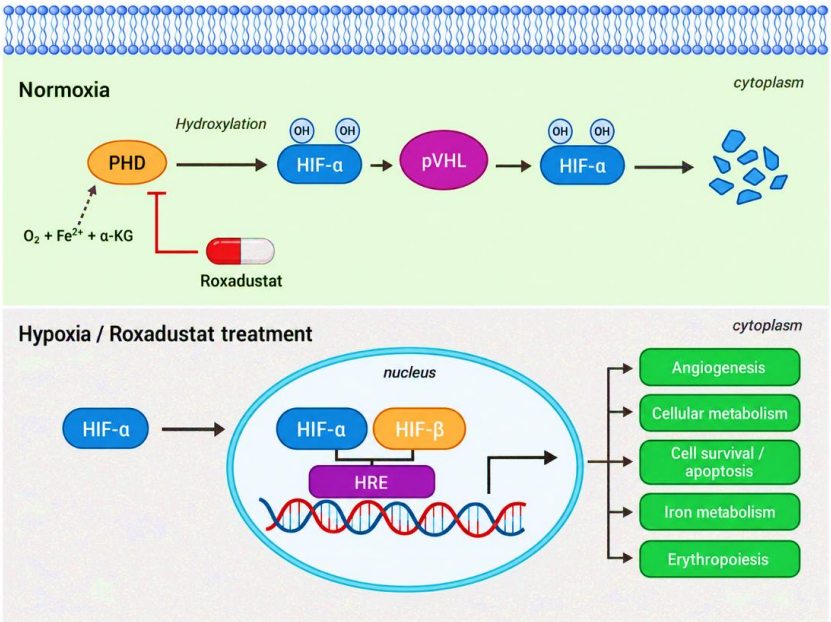
Under normoxic conditions, HIF-α is targeted for rapid proteasomal degradation. This process is initiated by a family of prolyl hydroxylase domain (PHD) enzymes, which utilize oxygen to hydroxylate specific proline residues on the HIF-α subunit. This hydroxylation creates a recognition site for the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex, which subsequently polyubiquitinates HIF-α, marking it for destruction. A parallel layer of inhibition is provided by the asparaginyl hydroxylase FIH-1, which hydroxylates an asparagine residue in the HIF-α transactivation domain, blocking its ability to recruit transcriptional coactivators like p300/CBP (Semenza, 2001; Yu et al., 2001).

In contrast, under hypoxic conditions, the reduced availability of oxygen limits the activity of the oxygen-dependent PHD and FIH-1 enzymes. This allows HIF-α to evade hydroxylation and degradation, leading to its accumulation and stabilization. The stabilized HIF-α translocates to the nucleus, dimerizes with HIF-1β, and binds to hypoxia-response elements (HREs) in the promoter regions of hundreds of target genes (Stolze et al., 2006). This initiates a robust transcriptional program governing key adaptive processes, including angiogenesis, energy metabolism, iron homeostasis, and cell survival.

Roxadustat pharmacologically mimics this hypoxic state. As a potent inhibitor of the PHD enzymes, it prevents the oxygen-dependent degradation of HIF-α even in the presence of normal oxygen levels. This results in the constitutive stabilization, nuclear accumulation, and subsequent transcriptional activation of the HIF pathway, thereby eliciting the wide-ranging biological effects that underpin its therapeutic potential beyond anemia (Semenza, 2001; Yang et al., 2021; Yu et al., 2001) (Figure 1).

Figure 1

HIF signaling cascade and downstream therapeutic target



Note: PHD prolyl hydroxylase domain; HRE: hypoxia-response element; pVHL: protein von Hippel-Lindau.

Non-Hematopoietic effects of Roxadustat

Roxadustat has been well established as a stabilizer of HIF-α, leading to robust EPO induction and successful clinical application in treating renal anemia, particularly in patients with CKD (Yang et al., 2021). While its hematopoietic benefits are well recognized, accumulating evidence indicates that HIF activation regulates nearly a hundred downstream genes. The broader physiological consequences of Roxadustat on these non-erythropoietic pathways, however, remain incompletely defined.

Angiogenesis

Beyond its established role in erythropoiesis, Roxadustat demonstrates potent pro-angiogenic properties, positioning it as a potential therapeutic agent for ischemic disorders. The molecular basis for this effect lies in the function of HIF as a master transcriptional regulator of angiogenesis. Under hypoxic conditions, HIF directly orchestrates the upregulation of a comprehensive suite of pro-angiogenic genes, including critical growth factors like VEGF and Platelet-Derived Growth Factor B (PDGF-B), as well as matrix metalloproteinases (MMPs) that facilitate tissue remodeling (Naito et al., 2020). Collectively, these effectors synergize to drive all stages of neovascularization, from endothelial cell activation and migration to the formation and stabilization of mature blood vessels.

Roxadustat pharmacologically recapitulates this process by stabilizing HIF-1α under normoxic conditions, and its pro-angiogenic efficacy is substantiated by compelling evidence from diverse preclinical models. For instance, in tissue engineering chamber studies, Roxadustat-loaded scaffolds significantly enhanced neovascular density and maturity, where it improved microcirculatory perfusion and markedly increased flap survival through the upregulation of HIF-1α/VEGF signaling (Lan et al., 2023). Furthermore, in the context of organ protection, Roxadustat administration to neonatal mice with hyperoxia-induced lung injury preserved alveolar structure by augmenting pulmonary vascular density via the upregulation of VEGF and endothelial nitric oxide synthase (eNOS) (Huang et al., 2021). These findings underscore that the angiogenic capacity of Roxadustat could broaden its therapeutic applications well beyond the correction of anemia. This positions HIF prolyl hydroxylase inhibition as a novel and promising strategy for promoting ischemic tissue repair and enhancing vascular protection across a range of pathological conditions.

Cellular metabolic reprogramming

Another profound systemic effect of HIF activation is the reprogramming of cellular metabolism. HIF is the master regulator that shifts cellular energy production toward anaerobic glycolysis, even in the presence of oxygen (Vaupel & Multhoff, 2021). By stabilizing HIF, Roxadustat pharmacologically induces this metabolic shift. It achieves this primarily by upregulating key effectors such as the glucose transporter GLUT1, the rate-limiting glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), and lactate dehydrogenase A (LDHA), which collectively enhance glycolytic flux (Kasprzak, 2021; Liu et al., 2022; Nishioku et al., 2025).

Experimental evidence from various cell types corroborates this metabolic reprogramming effect. In human primary myotubes, Roxadustat significantly increased glycolytic activity in cells from both normal glucose tolerance (1.4-fold) and type 2 diabetic donors (1.7-fold), an effect driven by HIF-mediated upregulation of GLUT1, HK2, and other enzymes that enhance glucose uptake (Mäkinen et al., 2024). Similarly, in cardiomyocytes under hypoxia, Roxadustat reversed the suppression of glycolysis caused by the ketone body β-hydroxybutyrate (β-OHB), restoring the expression of GLUT1, PFKFB3, and LDHA to reinstate vital ATP production (Ma et al., 2022). Furthermore, in retinal pigment epithelial (RPE) cells damaged by cigarette smoke extract, Roxadustat counteracted the induced metabolic impairment by stabilizing HIF-1α, thereby rescuing both basal and compensatory glycolytic function (Henning et al., 2023; Jacquemin et al., 2024; Lin et al., 2021).

The ability to enhance glycolytic flux suggests that Roxadustat possesses significant therapeutic potential in protecting ischemic tissues, namely the heart, brain, and kidney, from energy failure during hypoxic insults. However, this potent metabolic reprogramming serves as a double-edged sword, as evidenced by reports of metabolic imbalances in retinal cells (Nsiah et al., 2023). More critically, within a tumor microenvironment, the promotion of glycolysis may inadvertently facilitate cancer cell proliferation and chemoresistance (Qannita et al., 2024). These divergent outcomes underscore the critical need for careful patient stratification and monitoring of both glucose homeostasis and oncologic status when utilizing HIF prolyl hydroxylase inhibitors.

Cell survival and apoptosis

Roxadustat also modulates cell survival and apoptosis, conferring cytoprotection through several context-dependent mechanisms. These effects are particularly prominent in renal, cardiac, and hematopoietic tissues subjected to ischemic or toxic insults. The primary anti-apoptotic mechanism involves the activation of adaptive autophagy and mitophagy via the HIF-1α/BNIP3 signaling axis. For instance, Roxadustat protected bone marrow stromal cells from oxygen-glucose deprivation–induced apoptosis by engaging this pathway (Chen et al., 2022). Similarly, it mitigated

contrast-induced apoptosis in renal tubular cells through HIF-1α-dependent, BNIP3-mediated mitophagy, an effect that was abrogated in the absence of BNIP3 (Lin et al., 2021).

Beyond autophagy, Roxadustat has been shown to suppress pro-apoptotic signaling by inhibiting the transforming growth factor-beta 1 (TGF-β1)/Smad3 pathway in hypoxic renal cells (Zheng et al., 2023). Furthermore, its protective effects can be amplified through synergy with other agents; when combined with the SGLT2 inhibitor dapagliflozin, Roxadustat enhanced survival signaling via the PI3K/Akt/mTOR pathway in both renal and cardiac tissues (Sung et al., 2024).

However, these cytoprotective properties are not universal and appear highly dependent on the pathological context. In a model of chronic fibrosis via unilateral ureteral obstruction (UUO), for example, Roxadustat failed to significantly reduce apoptosis and was even associated with a transient upregulation of pro-fibrotic markers at high doses (Kabei et al., 2020). This finding highlights a critical limitation, suggesting that its benefits may be diminished or absent in settings of established, progressive fibrosis.

Regulation of iron metabolism

A cornerstone of Roxadustat's mechanism is its profound impact on iron metabolism, which has therapeutic implications for conditions of iron dysregulation. The primary driver of these effects is the HIF-mediated suppression of hepcidin, the master hormonal regulator of systemic iron. By lowering hepcidin levels, Roxadustat promotes duodenal iron absorption and facilitates the release of iron from macrophages and hepatocytes (Ganz et al., 2023). This fundamental shift in iron handling manifests clinically as increased serum iron, total iron-binding capacity (TIBC), and transferrin levels, with a corresponding decrease in the iron storage protein, ferritin. While transferrin saturation (TSAT) can be variable—reflecting the dynamic balance between iron mobilization and its consumption for erythropoiesis—a key clinical outcome is the significant reduction in the need for intravenous iron supplementation in patients with CKD and post-transplant anemia (Chen et al., 2019; Hirai et al., 2023; Hou et al., 2022; Wang et al., 2022).

Table 1 summarizes the key mechanisms and signaling pathways by which Roxadustat exerts its effects across different disease contexts, providing a mechanistic framework for interpreting the preclinical evidence discussed in the following section.

Preclinical evidence

Preclinical studies demonstrate that HIF stabilization by Roxadustat confers broad therapeutic benefits across multiple organ systems. Experimental models have revealed protective and reparative effects in cardiovascular, neurological, metabolic, renal, hepatic, and oncological contexts, underscoring the pleiotropic potential of HIF pathway modulation.

Cardiovascular diseases

The pleiotropic effects of Roxadustat confer significant therapeutic potential in cardiovascular diseases, a domain where its benefits may extend well beyond anemia correction. Compelling preclinical evidence suggests that Roxadustat exerts direct cardioprotective effects across multiple models. In the context of myocardial infarction, it mitigates ischemic injury by enhancing angiogenesis, improving metabolic adaptation, and attenuating oxidative stress (Madai et al., 2024). Its utility has also been demonstrated in diabetic cardiomyopathy by improving cardiac function (Fang et al., 2025) and in ameliorating adverse cardiac remodeling post-injury (Zaruba et al., 2024). Furthermore, Roxadustat appears to counteract hypertension-related cardiac damage by modulating angiotensin receptor signaling and enhancing endothelial nitric oxide synthase (eNOS) activity (Yu et al., 2021).

These promising preclinical findings are supported by emerging clinical data. A recent meta-analysis of anemic CKD patients, for instance, reported that treatment with Roxadustat was associated with a reduced risk of major adverse cardiovascular events (MACE) when compared to conventional ESAs (Li et al., 2024). However, these potential benefits must be weighed against important safety considerations. The pro-hypertensive effects of HIF activation remain a concern, with some studies indicating an elevated risk of hypertension (Zhang, et al., 2024). In addition, an increased risk of hyperkalemia is observed versus placebo, necessitating intensive electrolyte monitoring and medication review in CKD patients, particularly those receiving concurrent RAAS inhibitors (Bartnicki, 2024). Moreover, the potential for a pro-thrombotic state, possibly linked to the upregulation of platelet activation proteins, requires careful evaluation. Therefore, large-scale, long-term cardiovascular outcome trials are essential to definitively establish the net risk-benefit profile of Roxadustat in both renal and non-renal patient populations.

Neuroprotection

The activation of HIF signaling by Roxadustat also confers significant neuroprotection, with potential applications in both acute ischemic and chronic neurodegenerative conditions. The therapeutic promise of Roxadustat is particularly evident in models of acute ischemic stroke, where it mitigates neuronal death and reduces infarct volume through a

multi-pronged mechanism. This includes enhancing the survival of transplanted bone marrow stromal cells (BMSCs) and activating adaptive autophagy via the HIF-1α/BNIP3 pathway (Long et al., 2020; Moreton et al., 2023). Concurrently, Roxadustat promotes favorable metabolic reprogramming by upregulating glycolytic enzymes (Madai et al., 2024) and counteracts oxidative stress by activating the HIF-1α/NRF2 antioxidant response (Jiao et al., 2024).

These effects align with the broader concept of pharmacological preconditioning, where activating endogenous stress-response pathways enhances cerebral resilience against ischemic insults. This strategy has shown promise in other experimental stroke models (Nik Ramli et al., 2015), reinforcing the rationale for using HIF stabilizers to induce a neuroprotective state. Beyond acute injury, the benefits of Roxadustat extend to models of chronic neurological disorders. In experimental migraine, it has been shown to elevate pain thresholds via the HIF-1α/NF-κB signaling pathway (Yang et al., 2023), while in models of Parkinson's disease, it counteracts α-synuclein-induced toxicity through the activation of the cytoprotective HIF-1α/heme oxygenase-1 (HO-1) axis (Fujimaki et al., 2023).

Table 1

Mechanisms and pathways of Roxadustat in different diseases.

Disease area		Key effects	Primary mechanisms
Cardiovascular		↓ MI injury, ↑ Cardiac function, ↓ MACE risk (vs ESA)	Angiogenesis ↑, Oxidative stress ↓, eNOS activity ↑
Nervous system diseases		↓ Neuronal death, ↑ Pain threshold, ↓ α-Syn toxicity	HIF-1α → BNIP3/NF-κB/HO-1
Metabolic diseases		↓ LDL-C/TC, ↓ TSH, Renoprotection	Chol. synthesis ↓ & clearance ↑, T3 mimicry
Bone		↓ Osteoporosis, ↓ iPTH/FGF23	Wnt/β-catenin pathway ↑
Vascular calcification		↓ Calcification area	HIF-2α → ↓ Osteogenic differentiation
Acute Kidney Injury		Renoprotection (↓ Scr, BUN, KIM-1)	EPO/VEGF ↑, Inflammation ↓, Apoptosis ↓
Liver Disease		↑ Lipid oxidation, ↓ Liver inflammation	SREBP1c ↓, PPARα/CPT1A ↑
Onco-logy	Anti-Tumor	↑ Cell death (Necrosis/Ferroptosis), ↑ Immunotherapy	HIF→Metabolic/Immune reprogramming, Vasculature normalization
	Pro-Tumor	Risk: ↑ Tumor progression (e.g., PCa metastasis)	HIF-1α → STAT3 → MIF → IL-6/CXCL5 ↑

Notes: Abbreviations: ↑: Increase/Enhance; ↓: Decrease/Inhibit; →: Leads to/Activates; MI: Myocardial In farction; MACE: Major Adverse Cardiovascular Events; ESA: Erythropoiesis-Stimulating Agent; eNOS: endothelial Nitric Oxide Syn thase; α-Syn: Alpha-Synuclein; LDL-C: Low-Density Lipoprotein Cholesterol; TC: Total Cholesterol; TSH: Thyroid-Stimulating Hormone; T3: Triiodothyronine; iPTH: intact Parathyroid Hormone; FGF23: Fibroblast Growth Factor 23; Scr: Serum Creatinine; BUN: Blood Urea Nitrogen; KIM-1: Kidney Injury Molecule-1; EPO: Erythropoietin; VEGF: Vascular Endothelial Growth Factor; SREBP1c: Sterol Regulatory Element-Binding Transcription Factor 1; PPARα: Peroxisome Proliferator-Activated Receptor Alpha; CPT1A: Carnitine Palmitoyltransferase 1A; PCa: Prostate Cancer; MIF: Macrophage Migration Inhibitory Factor; IL-6: Interleukin 6; CXCL5: C-X-C Motif Chemokine Ligand.

Metabolic disorders

Beyond its hematologic effects, Roxadustat is emerging as a potent modulator of metabolic disorders, with significant therapeutic potential in diabetes and dyslipidemia. In the context of diabetic nephropathy, it confers renal protection by stabilizing HIF-1α and HIF-2α, which enhances glomerular endothelial cell viability, suppresses apoptosis, and alleviates the underlying renal hypoxia that drives disease progression (Fang et al., 2023; Xie et al., 2019). Concurrently, Roxadustat exerts a significant influence on lipid regulation, consistently lowering atherogenic lipids like total cholesterol and low-density lipoprotein cholesterol (LDL-C) (Hirai et al., 2023; Wang et al., 2022; Xu et al., 2025) through a dual mechanism of inhibiting cholesterol synthesis and upregulating clearance receptors.

Improvement of bone metabolism and osteoporosis

Roxadustat is also emerging as a potential modulator of bone metabolism and osteoporosis, with promising effects observed in preclinical models of both primary and secondary bone disease. Preclinical studies demonstrate that it can prevent estrogen deficiency-induced osteoporosis by activating critical osteogenic pathways, such as the Wnt/β-catenin signaling cascade, to promote bone formation (Li et al., 2022).

Furthermore, in the context of CKD, Roxadustat has been shown to ameliorate renal osteodystrophy. It achieves this by favorably modulating the balance of bone remodeling while also significantly reducing serum levels of intact parathyroid hormone (iPTH) and fibroblast growth factor 23 (FGF23). This hormonal regulation helps mitigate the adverse skeletal effects driven by secondary hyperparathyroidism (Li et al., 2023). Together, these findings suggest that HIF stabilization may offer a novel therapeutic approach for treating complex bone disorders.

Alleviation of vascular calcification

Roxadustat may also play a crucial role in mitigating vascular calcification, a major driver of cardiovascular morbidity in CKD. This potential was demonstrated in a preclinical CKD model using 5/6 nephrectomized rats on a pro-calcific, high-calcium/phosphate diet. In this model, the administration of Roxadustat (10 mg/kg thrice weekly for 4 weeks) led to a significant reduction in the total area of vascular calcification. The protective effect is attributed to a sophisticated, dual mechanism mediated by distinct HIF subunits. On one hand, HIF-2α activation was found to directly inhibit the osteogenic trans-differentiation of vascular smooth muscle cells (VSMCs), suppressing key markers like BMP2 and Runx2. Concurrently, the process involved the downregulation of HIF-1α, which in turn suppressed the expression of pro-calcific mediators like endothelin-1 (Wang et al., 2024). This discovery not only highlights a novel therapeutic application for Roxadustat in managing CKD-associated vascular pathology but also uncovers a complex interplay between HIF isoforms in regulating vascular health.

Acute Kidney Injury (AKI)

Roxadustat has demonstrated significant renoprotective effects in preclinical models of Acute Kidney Injury (AKI), including those induced by ischemia-reperfusion, cisplatin, and contrast agents. The core mechanism involves PHD inhibition and subsequent HIF-α stabilization, which orchestrates a multifaceted defense against renal damage. This coordinated response consistently improves key markers of renal function by reducing serum creatinine (Scr), blood urea nitrogen (BUN), and kidney injury molecule-1 (KIM-1) while simultaneously mitigating histological evidence of tubular damage (Chen et al., 2024; Miao et al., 2021).

Mechanistically, Roxadustat first enhances the kidney's adaptation to hypoxic stress by upregulating protective factors like EPO and VEGF and by promoting a shift toward glycolysis for energy production (Yang et al., 2023; Zhang et al., 2022; Zhang et al., 2024). Concurrently, it exerts potent anti-inflammatory effects (Li & Nik Ramli, 2025). This is achieved by suppressing the AIM2 inflammasome via a CD73/adenosine-dependent pathway, which reduces the release of pro-inflammatory cytokines IL-1β and IL-18. It also diminishes the infiltration of macrophages and neutrophils into the injured tissue by downregulating mediators like TNF-α and MCP-1 (Miao et al., 2021; Yang et al., 2023).

A third critical component of its renoprotective action is the direct inhibition of apoptosis. Roxadustat attenuates programmed cell death by downregulating pro-apoptotic factors like Bax and caspase-12, while upregulating the anti-apoptotic protein Bcl-2. Furthermore, it promotes cellular resilience through HIF-1α/BNIP3-mediated mitophagy, a process that clears damaged mitochondria (Lin et al., 2021). Notably, the therapeutic efficacy of these mechanisms has been enhanced through novel delivery systems, such as renal-targeted tetrahedral framework nucleic acid (tFNA) complexes, which improve drug bioavailability and reduce potential off-target toxicity (Chen et al., 2024).

These interconnected mechanisms, which include the enhancement of hypoxia adaptation along with the suppression of inflammation and apoptosis, provide a robust defense against acute renal insults. This body of preclinical evidence supports the possibility of using Roxadustat prophylactically in high-risk scenarios such as prior to chemotherapy, contrast media administration, or organ transplantation (Lin et al., 2021).

Liver disease

The regulatory effects of Roxadustat extend to various forms of liver disease, where its impact is highly context-dependent, spanning from modest cytoprotection to significant metabolic correction and complex modulation of cancer cell biology. In models of acute surgical stress following partial hepatectomy, for instance, its effects were nuanced; while not significantly accelerating liver regeneration, it did alleviate stress-induced cellular injuries (Iesari et al., 2021). In stark contrast, Roxadustat demonstrated clear therapeutic efficacy in alcoholic liver disease (ALD), where it ameliorated hepatic lipid accumulation by inhibiting SREBP1c-mediated lipid synthesis while promoting fatty acid β-oxidation via the PPARα/CPT1A pathway, concurrently mitigating inflammation and oxidative stress (Gao et al., 2022). The drug's role in liver cancer is more complex, highlighting a dual potential within the tumor microenvironment. By

stabilizing HIF-1α/HIF-2α, Roxadustat induced a metabolic shift toward glycolysis that, while suppressing baseline cell proliferation, also enhanced the cancer cells' resistance to specific stressors like mitochondrial inhibitors (Jacquemin et al., 2024). Collectively, these findings illustrate that the therapeutic utility of HIF stabilization in the liver is not uniform, showing significant promise in metabolic and inflammatory conditions but requiring careful consideration in contexts of regeneration and oncology.

Oncology implications

The role of Roxadustat in oncology is complex and highly context-dependent, presenting a "double-edged sword" with both anti-tumor and pro-tumorigenic potential. On one hand, it can actively combat tumors through direct mechanisms and by enhancing anti-tumor immunity; on the other, its pro-survival signaling carries inherent risks that are supported by some preclinical models. This duality underscores the critical need for careful patient selection and a deep understanding of the underlying tumor biology.

The anti-tumor potential of Roxadustat is multifaceted. It can exert direct cytotoxic or sensitizing effects, such as inducing ferroptosis in temozolomide-resistant glioblastoma (Su et al., 2022)or accelerating necrosis in SDHB-mutant paragangliomas (Wang et al., 2023). In other models like Lewis lung carcinoma, it promotes vascular normalization, which improves tumor oxygenation and enhances sensitivity to chemotherapy and radiotherapy (Nishide et al., 2020). Beyond these direct actions, Roxadustat can fundamentally reprogram the tumor microenvironment to favor anti-tumor immunity. In models of immunotherapy-resistant colorectal cancer, for example, HIF-1α stabilization increased $CD8^+$ T cell infiltration and synergized powerfully with anti-PD-1 therapy to overcome resistance (Chen et al., 2025).

While this preclinical potential is compelling, the clinical picture and associated risks require a balanced assessment. Encouragingly, (Lu et al., 2025; Seeley et al., 2017). In models of prostate cancer bone metastasis, for instance, a HIF-1α-STAT3-MIF signaling axis was found to promote tumor progression (Mendoza-Reinoso et al., 2022). The general concern also remains that HIF stabilization could upregulate pro-angiogenic factors like VEGF in certain contexts (Gáll et al., 2025). This highlights that the ultimate oncological impact of Roxadustat is dictated by the specific tumor type and its microenvironment, demanding a highly individualized approach to its potential use in oncology.

Translational perspectives

While Roxadustat is currently approved for the treatment of renal anemia, a growing body of clinical evidence highlights its potential utility in a range of non-renal anemias. In patients with myelofibrosis, it has been shown to correct ruxolitinib-associated anemia, increase hemoglobin levels, reduce spleen volume, and even lower the JAK2 mutation burden (Ding et al., 2023). Its efficacy is also evident in aplastic anemia (AA), where it improves hematologic response rates in refractory cases, enables transfusion independence for some patients, and is generally well tolerated (Shi et al., 2024; Xu et al., 2024).

In low-risk myelodysplastic syndrome (LR-MDS), Roxadustat achieved an efficacy rate exceeding 52%, improving hemoglobin and hematocrit, lowering cholesterol, and showing particular benefit in patients with elevated baseline EPO levels (Lewis et al., 2021) . In chemotherapy-induced anemia (CIA), Roxadustat was non-inferior to recombinant human erythropoietin (rHuEPO-α), with the added advantage of oral administration and improved patient compliance (Lu et al., 2025). Similarly, in post-transplant anemia (PTA) following kidney transplantation, it increased hemoglobin levels, improved iron metabolism indices, preserved renal function, and maintained stable tacrolimus concentrations, while demonstrating a favorable safety profile (Kong et al., 2024).

Mechanistically, these benefits extend beyond erythropoietin induction. Roxadustat exerts additional effects through suppression of pro-inflammatory cytokines and regulation of iron utilization, contributing to its efficacy across different hematologic disorders. Reported adverse reactions are primarily mild to moderate gastrointestinal events, with no major safety risks identified to date (Zhu et al., 2022).

Despite these encouraging results, the evidence for Roxadustat in non-renal anemias remains preliminary. While the scientific rationale is strong and early data are promising, current findings are insufficient to support routine clinical use or regulatory approval. Larger, prospective randomized controlled trials will be essential to validate efficacy, clarify safety, and define patient populations most likely to benefit.

CONCLUSION

This review synthesizes compelling preclinical and translational evidence that Roxadustat's therapeutic potential extends significantly beyond its approved indication for renal anemia. By stabilizing hypoxia-inducible factor (HIF), Roxadustat activates a broad transcriptional program that confers beneficial effects on angiogenesis, metabolism, and tissue repair across multiple organ systems. These pleiotropic actions position it as a formidable candidate for repurposing in diverse non-hematologic conditions, including cardiovascular, neurological, metabolic, and select oncological diseases.

However, translating this broad potential into safe and effective therapies presents substantial challenges. The pleiotropic nature of HIF signaling necessitates careful patient stratification to align the drug's mechanism with the specific pathophysiology of a disease. Furthermore, significant safety concerns must be addressed, including the risk of tumor promotion in susceptible microenvironments, exacerbation of hypertension, induction of central hypothyroidism, and an increased thrombotic risk.

Ultimately, the journey of Roxadustat from a targeted anemia therapy to a broad-spectrum pleiotropic drug will depend on meticulously designed clinical trials that can navigate this complex risk-benefit landscape. Successfully harnessing the power of systemic hypoxia adaptation represents both a major challenge and a profound opportunity in modern pharmacology. By highlighting Roxadustat's potential to address unmet clinical needs, this review contributes directly to the advancement of SDG 3 (Good Health and Well-Being). Nevertheless, its future integration hinges on rigorous safety vetting and a responsible approach to therapeutic innovation.

LIST OF ABBREVIATIONS

HIF-PHI	Hypoxia-inducible factor prolyl hydroxylase inhibitor
CKD	Chronic kidney disease
HIF	Hypoxia-inducible factor
ESA	Erythropoiesis-stimulating agent
VEGF	Vascular Endothelial Growth Factor
GLUT-1	Glucose Transporter 1
PHD	Prolyl hydroxylase domain
VHL	von Hippel-Lindau
FIH-1	Factor inhibiting HIF-1
HRE	Hypoxia-response element
PDGF-B	Platelet-Derived Growth Factor B
MMP	Matrix metalloproteinase
eNOS	Endothelial nitric oxide synthase
LDHA	Lactate dehydrogenase A
PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3
β-OHB	β-hydroxybutyrate
RPE	Retinal pigment epithelial
BNIP3	BCL2/adenovirus E1B 19 kDa interacting protein 3
TGF-β1	Transforming growth factor-beta 1
SGLT2	Sodium-glucose cotransporter 2
PI3K	Phosphatidylinositol 3-kinase
Akt	Protein kinase B
mTOR	Mammalian target of rapamycin
UUO	Unilateral ureteral obstruction
TIBC	Total iron-binding capacity
TSAT	Transferrin saturation
MI	Myocardial Infarction
MACE	Major Adverse Cardiovascular Events
α-Syn	Alpha-Synuclein
LDL-C	Low-Density Lipoprotein Cholesterol
TC	Total Cholesterol
TSH	Thyroid-Stimulating Hormone
T3	Triiodothyronine
PTA	Post-transplant anemia
LR-MDS	Low-risk myelodysplastic syndrome
CIA	Chemotherapy-induced anemia
SREBP1c	Sterol Regulatory Element-Binding Transcription Factor 1
PPARα	Peroxisome Proliferator-Activated Receptor Alpha
CPT1A	Carnitine Palmitoyltransferase 1A
MIF	Macrophage Migration Inhibitory Factor
CXCL5	C-X-C Motif Chemokine Ligand 5
BMSC	Bone marrow stromal cell
LR-MDS	Low-risk myelodysplastic syndrome
CIA	Chemotherapy-induced anemia

AUTHOR CONTRIBUTIONS

The study was conceptualised and designed by Li Qinyun and Cheng Long. Resource acquisition was carried out by Li Qinyun and Cheng Long. The manuscript was reviewed by Nik Nasihah Nik Ramli. Final approval of the manuscript was done by Nik Nasihah Nik Ramli.

ETHICS APPROVAL

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Not applicable.

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