Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 12 July 2026
Revised 02 Aug 2026
Accepted 15 Aug 2026

Natural Resources for Human Health 2026, Vol. 6 (18s): 1292–1301

KEYWORDS:
Roxadustat, HIF-1α, HIF-2α, Erythropoiesis, Experimental anemia, Hematological recovery.

Effects of Roxadustat on HIF-1α and HIF-2α Expression and Hematological Recovery in a Rat Model of Experimental Anemia

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ABSTRACT: **Background**: Roxadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that promotes erythropoiesis through stabilization of hypoxia-inducible factors (HIFs). The present study evaluated the effects of Roxadustat on HIF-1α and HIF-2α expression and hematological recovery in experimental anemia.

Objective: In an experimental model of anemia induced by phenylhydrazine, the purpose of this study was to assess the dose-dependent effects of Roxadustat on HIF-1α and HIF-2α expression and hematological recovery.

Methods : Anemia was induced in the subjects through an intraperitoneal (i.p.) injection of phenylhydrazine (PHZ) (40 mg/kg body weight).Two days post-injection, we confirmed the model's success by evaluating hematological parameters, specifically hemoglobin (HGB) levels.The animals were divided into five groups: a healthy control group, an untreated anemia group, and three anemic groups treated orally with Roxadustat at doses of 10, 20, or 40 mg/kg/day for 14 consecutive days. Hematological parameters and the expression levels of HIF-1α and HIF-2α were subsequently evaluated.

Results : When anemia was induced, the RBC count and HCT significantly decreased in comparison to the control group. Hematological parameters were significantly improved by Roxadustat treatment in a dose-dependent manner; the group receiving 40 mg/kg had the highest HCT (48.00 ± 3.10%) and RBC count (7.47 ± 0.50 $\times 10^{12}$/L). Additionally, Roxadustat significantly and dose-dependently raised the expression of HIF-1α and HIF-2α. The 40 mg/kg group showed the highest expression levels, with HIF-1α at 4.06 ± 1.98 and HIF-2α at 5.08 ± 1.72. These results show progressive hematological recovery after Roxadustat treatment, along with increased activation of the HIF pathway.In addition ,antioxidant biomarkers including reduced glutathione (GSH) and superoxide dismutase (SOD) showed strong positive correlations with hemoglobin concentration ($r = 0.803$ and $r = 0.819$, respectively; $p < 0.01$).

Conclusion: Roxadustat effectively enhanced hematological recovery and increased HIF-1α and HIF-2α expression in experimental anemia in a dose-dependent manner. The 40 mg/kg dose produced the most pronounced hematological and molecular responses, supporting the role of HIF pathway activation in the erythropoietic effects of Roxadustat.

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INTRODUCTION

Roxadustat represents a novel class of orally administered therapeutic agents designed to treat anemia, particularly anemia associated with chronic kidney disease (CKD). It functions as a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI). By transiently inhibiting prolyl hydroxylase enzymes (PHDs), Roxadustat prevents the continuous degradation of HIF oxygen-sensitive subunits under normoxic conditions. This stabilization leads to the intracellular accumulation of HIF complexes, mimicking the physiological response to hypoxia and subsequently triggering the transcription of endogenous erythropoietin (EPO) [(1).]

The HIF alpha subunit exists primarily as two key isoforms involved in erythropoiesis: HIF-1α and HIF-2α. Although structurally similar, they regulate distinct target genes and display tissue-specific roles. While HIF-1α is ubiquitously expressed and drives metabolic adaptation, anaerobic glycolysis, and acute responses to hypoxia, HIF-2α is considered the primary physiological regulator of EPO gene expression in renal interstitial cells and hepatocytes. Furthermore, HIF-2α coordinates iron metabolism by enhancing intestinal iron absorption and mobilizing iron stores through the suppression of hepcidin [(2).]

The downstream objective of stabilizing the HIF pathway via Roxadustat is the significant improvement of peripheral hematological parameters, specifically Red Blood Cell (RBC) count and Hematocrit (HCT) levels. Clinical trials have demonstrated that HIF stabilization induces a gradual, controlled rise in hemoglobin and hematocrit, minimizing the need for high-dose intravenous iron supplementation. However,the effects of Roxadustat on HIF-1α and HIF-2α expression and their association with hematological recovery in experimental anemia remain an important area of investigation [(3).] Therefore, the present study aimed to evaluate the effects of Roxadustat on HIF-1α and HIF-2α expression and hematological recovery in a rat model of experimental anemia.

METHODOLOGY

An experimental animal study was conducted using healthy adult male Wistar rats weighing 180–200 g. The animals were randomly divided into five groups (n = 8 rats per group). Anemia was induced in rats using phenylhydrazine (PHZ) at a dose of 40 mg/kg/day administered intraperitoneally for two consecutive days. Two days post-injection, we confirmed the model's success by evaluating hematological parameters, specifically hemoglobin (HGB) levels. Following confirmation of anemia, the three treatment groups received Roxadustat orally for 14 consecutive days as follows:

1_Control Group: Received normal saline only , neither PHZ nor treatment.
2_Anemia Group: Received PHZ only.
3_Roxadustat 10 mg/kg Group: Anemic rats treated orally with Roxadustat at a dose of 10 mg/kg/day for 14 consecutive days.
4_Roxadustat 20 mg/kg Group: Anemic rats treated orally with Roxadustat at a dose of 20 mg/kg/day for 14 consecutive days.
5_Roxadustat 40 mg/kg Group: Anemic rats treated orally with Roxadustat at a dose of 40 mg/kg/day for 14 consecutive days.
Results

Effect of Roxadustat Treatment on Hematological Parameters in Experimental Anemia

Table 1 presents the effect of Roxadustat treatment on major hematological parameters, including red blood cell count (RBC), hemoglobin concentration (HGB), hematocrit (HCT), and reticulocyte percentage in experimentally induced anemia. The statistical analysis revealed highly significant differences among the studied groups for all evaluated hematological markers ($p < 0.001$), indicating a substantial influence of anemia induction and subsequent Roxadustat treatment on erythropoietic activity and blood profile recovery.

The anemia group demonstrated marked hematological deterioration compared with the control group, as evidenced by a significant reduction in RBC count, HGB concentration, and HCT percentage. Specifically, the anemia group recorded the lowest values for RBC ($3.75 \pm 0.19 \times 10^{12}$/L), HGB ($94.17 \pm 2.86$ g/L), and HCT ($27.00 \pm 1.41\%$), confirming successful induction of anemia and impairment of oxygen-carrying capacity. In contrast, reticulocyte percentage significantly increased in the anemia group ($2.55 \pm 0.19\%$), reflecting compensatory stimulation of bone marrow activity in response to reduced erythrocyte production and tissue hypoxia.

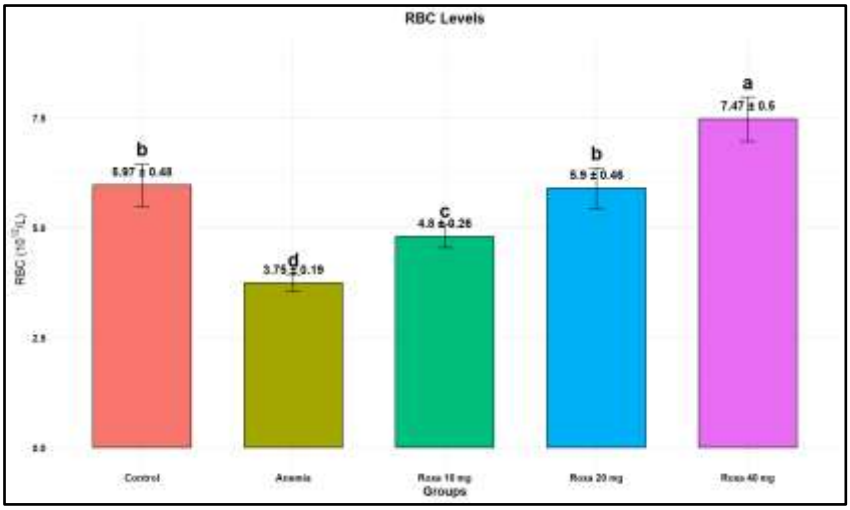
Administration of Roxadustat significantly improved hematological parameters in a dose-dependent manner. Treatment with Roxadustat 10 mg partially restored RBC count, hemoglobin level, and hematocrit percentage, suggesting moderate stimulation of erythropoiesis and recovery from anemia. More pronounced improvement was observed in the Roxadustat (20 mg) group, where hematological values approached those of the control group, particularly for RBC and HGB parameters.

Notably, the Roxadustat (40 mg) group exhibited the highest hematological values among all experimental groups, recording RBC, HGB, and HCT values of (7.47 ± 0.50 $\times 10^{12}$/L, 153.50 ± 5.58 g/L), and (48.00 ± 3.10%), respectively. These findings indicate strong activation of erythropoietic pathways and substantial enhancement of red blood cell production at higher Roxadustat doses. Similarly, reticulocyte percentage progressively increased with increasing treatment dose, reaching (5.37 ± 0.42%) in the Roxadustat (40 mg) group, which may reflect intensified bone marrow stimulation and accelerated erythrocyte regeneration.

Table 1. Effect of Roxadustat Treatment on Hematological Parameters

Groups	RBC ($\times 10^{12}$/L)	HGB (g/L)	HCT (%)	Reticulocyte (%)
Group 1	5.97 ± 0.48 ^{b}	127.83 ± 5.19 ^{b}	35.00 ± 1.17 ^{bc}	1.05 ± 0.10 ^{e}
Group 2	3.75 ± 0.19 ^{d}	94.17 ± 2.86 ^{d}	27.00 ± 1.41 ^{d}	2.55 ± 0.19 ^{d}
Group 3	4.80 ± 0.26 ^{c}	112.83 ± 5.00 ^{c}	33.67 ± 1.63 ^{c}	3.33 ± 0.22 ^{c}
Group 4	5.90 ± 0.46 ^{b}	127.50 ± 4.42 ^{b}	38.00 ± 1.90 ^{b}	4.40 ± 0.29 ^{b}
Group 5	7.47 ± 0.50 ^{a}	153.50 ± 5.58 ^{a}	48.00 ± 3.10 ^{a}	5.37 ± 0.42 ^{a}
p-value	<0.001	<0.001	<0.001	<0.001

Different letters within the same column indicate significant differences among groups at $p < 0.05$ according to Tukey's HSD test.



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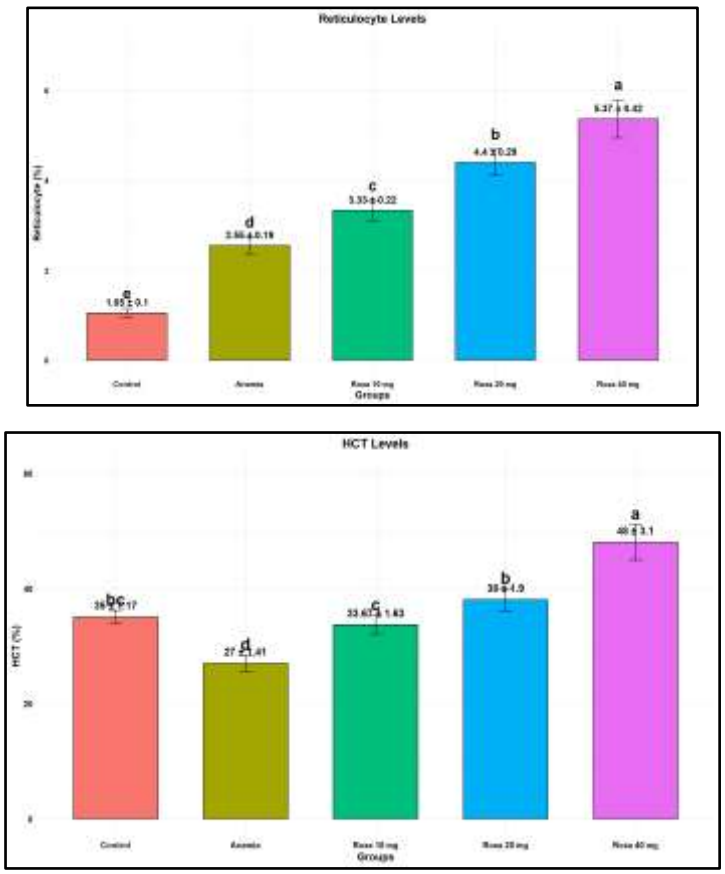


Figure (1): Effect of Roxadustat Treatment on Hematological Parameters in Experimental Anemia

Effect of Roxadustat Treatment on HIF Pathway Biomarkers in Experimental Anemia

Table 2 illustrates the effect of Roxadustat treatment on hypoxia-inducible factor biomarkers, including HIF-1α and HIF-2α expression levels, among the experimental groups. The statistical analysis revealed significant differences among groups for both HIF-1α and HIF-2α expression ($p = 0.001$ and $p < 0.001$, respectively), indicating that Roxadustat treatment markedly influenced activation of the HIF signaling pathway in a dose-dependent manner.

The control group exhibited baseline physiological expression levels for both HIF-1α and HIF-2α, with values of 1.00 ± 0.00. Mild elevations in HIF biomarker expression were observed in the anemia group and Roxadustat 10 mg group; however, these groups remained statistically similar according to Tukey's post hoc analysis. The anemia group recorded HIF-1α and HIF-2α expression values of 1.43 ± 0.89 and 1.51 ± 0.38, respectively, suggesting activation of compensatory hypoxic signaling pathways in response to reduced oxygen availability associated with anemia.

More pronounced activation of the HIF pathway was observed following administration of higher Roxadustat doses. The Roxadustat 20 mg group demonstrated significant increases in HIF-1α and HIF-2α expression compared with the control and lower-dose groups, reaching values of 3.25 ± 1.66 and 3.00 ± 0.82, respectively. This finding indicates enhanced stabilization of hypoxia-inducible factors and stimulation of downstream erythropoietic signaling pathways.

Notably, the Roxadustat 40 mg group exhibited the highest expression levels of both HIF biomarkers, recording HIF-1α and HIF-2α values of 4.06 ± 1.98 and 5.08 ± 1.72, respectively. These marked elevations strongly suggest potent activation of the HIF regulatory pathway at higher therapeutic doses of Roxadustat. The greater increase observed in HIF-2α expression compared with HIF-1α may indicate a more dominant role of HIF-2α in erythropoietin regulation and erythropoietic stimulation under Roxadustat treatment conditions.

The observed enhancement in HIF biomarker expression is biologically important because Roxadustat functions as a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), leading to stabilization of HIF proteins under normoxic

conditions. Stabilized HIF transcription factors subsequently activate genes involved in erythropoiesis, iron metabolism, oxygen transport, and cellular adaptation to hypoxia. Therefore, the progressive increase in HIF pathway activation observed across treatment groups may explain the concomitant improvements in erythropoietin production, hematological parameters, and iron profile biomarkers identified in the present study.

Overall, these findings demonstrate that Roxadustat effectively activates the HIF signaling pathway in a dose-dependent manner, with the 40 mg dose producing the strongest molecular response and potentially contributing to the therapeutic correction of experimental anemia.

Table 2. Effect of Roxadustat Treatment on HIF Pathway Biomarkers

Groups	HIF-1α Expression	HIF-2α Expression
Group 1	1.00 ± 0.00 c	1.00 ± 0.00 c
Group 2	1.43 ± 0.89 c	1.51 ± 0.38 c
Group 3	1.65 ± 0.68 c	1.97 ± 0.55 c
Group 4	3.25 ± 1.66 b	3.00 ± 0.82 b
Group 5	4.06 ± 1.98 a	5.08 ± 1.72 a
p-value	0.001	<0.001

Different letters within the same column indicate significant differences among groups at $p < 0.05$ according to Tukey's HSD test.

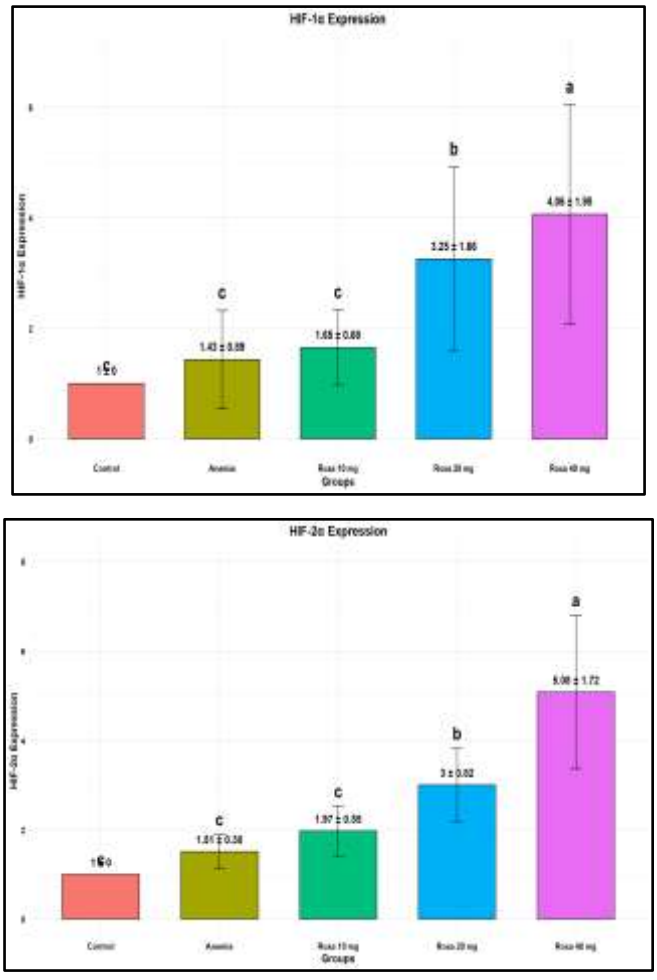


Figure 2 :Effect of Roxadustat Treatment on HIF Pathway

Correlation between Oxidative Stress Markers and Hemoglobin Level

Table 3 demonstrates significant correlations between oxidative stress biomarkers and hemoglobin concentration. Malondialdehyde (MDA), which represents lipid peroxidation and oxidative cellular damage, exhibited a strong negative correlation with hemoglobin levels ($r = -0.815$, $p < 0.01$). This finding indicates that increased oxidative stress is associated with reduced hemoglobin concentration and worsening anemia status. The observed reduction in hemoglobin may be attributed to oxidative damage affecting erythrocyte membrane integrity and shortening red blood cell lifespan.

In contrast, antioxidant biomarkers including reduced glutathione (GSH) and superoxide dismutase (SOD) showed strong positive correlations with hemoglobin concentration ($r = 0.803$ and $r = 0.819$, respectively; $p < 0.01$). These findings suggest that enhanced antioxidant defense mechanisms may contribute to preservation of erythrocyte stability and improvement of hemoglobin synthesis. The positive association between antioxidant activity and hemoglobin level further supports the hypothesis that reduction of oxidative stress plays an important role in alleviating anemia severity.

Collectively, these results indicate that oxidative stress has a substantial impact on hematological status, whereas antioxidant protection appears to support recovery of hemoglobin concentration in experimental anemia conditions.

Table 3: Pearson Correlation between Oxidative Stress Biomarkers and Hemoglobin Concentration

Variables	MDA (nmol/mL)	GSH (µmol/L)	SOD (U/mL)	HGB (g/L)
MDA (nmol/mL)	**1**	**-0.840****	**-0.867****	**-0.815****
GSH (µmol/L)	**-0.840****	**1**	**0.835****	**0.803****
SOD (U/mL)	**-0.867****	**0.835****	**1**	**0.819****
HGB (g/L)	**-0.815****	**0.803****	**0.819****	**1**

**** Correlation is significant at the 0.01 level (2-tailed).**

Correlation between Oxidative Stress Markers and Red Blood Cell Count

The correlation analysis presented in Table 4 revealed a significant relationship between oxidative stress markers and red blood cell (RBC) count. MDA showed a strong negative correlation with RBC count ($r = -0.814$, $p < 0.01$), indicating that elevated oxidative damage is associated with a decline in erythrocyte number. This reduction may result from oxidative injury to red blood cell membranes, increased hemolysis, and impaired cellular survival under anemic conditions.

Conversely, GSH and SOD demonstrated significant positive correlations with RBC count ($r = 0.808$ and $r = 0.822$, respectively; $p < 0.01$). The positive association suggests that antioxidant defense systems play a protective role in maintaining erythrocyte viability and reducing oxidative destruction of red blood cells. Higher antioxidant activity may therefore contribute to improved erythropoiesis and stabilization of circulating RBC levels.

These findings collectively emphasize the close interaction between oxidative stress and erythrocyte homeostasis. The results also support the possibility that therapeutic modulation of oxidative stress pathways may improve hematological recovery during anemia treatment.

Table 4: Pearson Correlation between Oxidative Stress Biomarkers and RBC Count

Variables	MDA (nmol/mL)	GSH (µmol/L)	SOD (U/mL)	RBC ($\times 10^{12}$/L)
MDA (nmol/mL)	1	-0.840**	-0.867**	-0.814**
GSH (µmol/L)	-0.840**	1	0.835**	0.808**
SOD (U/mL)	-0.867**	0.835**	1	0.822**
RBC ($\times 10^{12}$/L)	-0.814**	0.808**	0.822**	1

**** Correlation is significant at the 0.01 level (2-tailed).**

Correlation between Oxidative Stress Markers and Erythropoietin Level

Table 5 illustrates significant associations between oxidative stress biomarkers and erythropoietin (EPO) levels. MDA demonstrated a very strong positive correlation with EPO concentration ($r = 0.936$, $p < 0.01$), suggesting that elevated oxidative stress and tissue hypoxic injury may stimulate compensatory erythropoietin production. This increase in EPO likely reflects a physiological response aimed at restoring oxygen-carrying capacity during anemia progression.

On the other hand, antioxidant biomarkers GSH and SOD showed significant negative correlations with EPO levels ($r = -0.800$ and $r = -0.919$, respectively; $p < 0.01$). These findings may indicate that improved antioxidant defense reduces oxidative and hypoxic stress, thereby lowering the physiological stimulus for excessive erythropoietin secretion.

The observed relationships support the concept that oxidative stress is closely linked to erythropoietic regulation. Increased oxidative injury appears to activate compensatory EPO production, whereas restoration of antioxidant balance may contribute to normalization of erythropoietin levels following therapeutic intervention.

Table 5: Pearson Correlation between Oxidative Stress Biomarkers and EPO Level

Variables	MDA (nmol/mL)	GSH (µmol/L)	SOD (U/mL)	EPO (pg/mL)
MDA (nmol/mL)	1	-0.840**	-0.867**	0.936**
GSH (µmol/L)	-0.840**	1	0.835**	-0.800**
SOD (U/mL)	-0.867**	0.835**	1	-0.919**
EPO (pg/mL)	0.936**	-0.800**	-0.919**	1

**** Correlation is significant at the 0.01 level (2-tailed).**

Correlation between Oxidative Stress Markers and HIF-1α Expression

The results shown in Table 6 indicate weak and statistically non-significant correlations between oxidative stress biomarkers and HIF-1α expression. MDA exhibited a weak negative correlation with HIF-1α expression ($r = -0.246$, $p = 0.190$), whereas

GSH and SOD demonstrated weak positive correlations (r = 0.272 and r = 0.196, respectively), with no statistical significance observed ($p > 0.05$).

These findings suggest that HIF-1α expression may not be directly influenced by oxidative stress biomarkers under the current experimental conditions. Although oxidative stress and hypoxia are biologically interconnected processes, the regulation of HIF-1α appears to involve multiple signaling pathways and molecular mediators beyond the measured oxidative parameters alone.

The absence of significant associations may also indicate that HIF-1α activation is more strongly related to hypoxic signaling induced by anemia or pharmacological stimulation by Roxadustat rather than direct oxidative stress status. Therefore, additional molecular investigations may be required to further clarify the mechanistic relationship between oxidative stress and HIF pathway activation in experimental anemia.

Table 6: Pearson Correlation between Oxidative Stress Biomarkers and HIF-1α Expression

Variables	MDA (nmol/mL)	GSH (µmol/L)	SOD (U/mL)	HIF-1α Expression
MDA (nmol/mL)	**1**	**-0.840****	**-0.867****	**-0.246**
GSH (µmol/L)	**-0.840****	**1**	**0.835****	**0.272**
SOD (U/mL)	**-0.867****	**0.835****	**1**	**0.196**
HIF-1α Expression	**-0.246**	**0.272**	**0.196**	**1**

**** Correlation is significant at the 0.01 level (2-tailed).**

The hematological findings revealed significant recovery of RBC count, hematocrit percentage, and reticulocyte production following Roxadustat administration. The highest therapeutic efficacy was consistently observed in the Roxadustat 40 mg group, which produced values approaching or exceeding those of the healthy control group.

Furthermore, Roxadustat significantly activated the HIF signaling pathway, particularly HIF-1α and HIF-2α expression, supporting its mechanism of action as a hypoxia-inducible factor prolyl hydroxylase inhibitor. Correlation analyses confirmed that oxidative stress plays an important role in anemia progression, as elevated MDA was strongly associated with reduced hemoglobin and RBC levels, whereas antioxidant biomarkers showed positive relationships

DISCUSSION

The present study demonstrated that Roxadustat treatment produced a clear dose-dependent improvement in hematological parameters in rats with experimentally induced anemia. The untreated anemia group showed marked reductions in red blood cell (RBC) count, hemoglobin concentration, and hematocrit (HCT) compared with the healthy control group, confirming successful induction of anemia. The accompanying increase in reticulocyte percentage reflects a compensatory bone marrow response to reduced oxygen-carrying capacity and tissue hypoxia [4-5]

Administration of Roxadustat progressively improved the hematological profile, with greater responses observed as the treatment dose increased. The 10 mg/kg dose produced partial recovery, while the 20 mg/kg dose resulted in further improvement toward normal hematological values. The most pronounced response was observed with 40 mg/kg Roxadustat, which produced the highest RBC count, hematocrit, and reticulocyte percentage among the experimental groups. These findings indicate enhanced erythropoietic activity following Roxadustat administration and are consistent with previous studies demonstrating that HIF-prolyl hydroxylase inhibition can stimulate erythropoiesis and improve hematological parameters in anemia [6-7]

The molecular findings further support the hematological response observed in the present study. Roxadustat increased the expression of both HIF-1α and HIF-2α in a dose-dependent manner, with the highest expression levels detected in the 40 mg/kg treatment group. In contrast, experimental anemia alone produced only a mild increase in HIF expression. These findings are consistent with the established pharmacological mechanism of Roxadustat as a hypoxia-inducible factor prolyl hydroxylase inhibitor, which stabilizes HIF proteins by reducing their oxygen-dependent degradation

Stabilization of the HIF pathway has important consequences for erythropoiesis. Previous studies have shown that activation of hypoxia-responsive pathways promotes endogenous erythropoietin production and regulates processes involved in iron availability and utilization [8]. In the present study, the progressive elevation of HIF-1α and HIF-2α expression across the Roxadustat-treated groups occurred together with improvement in RBC count, hematocrit, and reticulocyte production. This parallel response supports the involvement of HIF pathway activation in the hematological recovery observed following Roxadustat treatment.

In addition to the principal hematological and molecular findings, the correlation analyses provided supportive information regarding oxidative stress and hematological status. MDA showed strong negative correlations with hemoglobin concentration and RBC count, whereas the antioxidant biomarkers GSH and SOD showed strong positive correlations with these hematological parameters. These findings suggest that increased oxidative stress is associated with poorer hematological status, whereas greater antioxidant activity is associated with preservation and recovery of erythrocyte parameters. Similar relationships between oxidative imbalance and erythrocyte damage have been described in previous studies [9–10]

The relationship between oxidative stress biomarkers and erythropoietin provided additional insight into the response to experimental anemia. MDA showed a strong positive correlation with EPO, whereas GSH and SOD were negatively correlated with EPO. This pattern may reflect greater compensatory erythropoietin stimulation under conditions characterized by increased oxidative and hypoxic stress [11-12]. However, because these findings represent statistical associations, they should not be interpreted as evidence of a direct causal relationship between oxidative stress and EPO regulation.

In contrast to the significant relationships observed with hematological parameters and EPO, oxidative stress biomarkers showed only weak and statistically non-significant correlations with HIF-1α expression. This finding suggests that variation in HIF-1α expression in the present experimental model was not directly associated with the measured oxidative stress biomarkers. Because Roxadustat directly inhibits prolyl hydroxylase enzymes involved in HIF degradation, pharmacological HIF stabilization may have had a greater influence on HIF-1α expression than variations in the measured oxidative stress markers [13-14]. Further mechanistic studies would be required to establish the relationship between these pathways.

Taken together, the present findings demonstrate that Roxadustat promotes dose-dependent hematological recovery accompanied by increased HIF-1α and HIF-2α expression in experimental anemia. The strongest hematological and molecular responses were observed with the 40 mg/kg dose, supporting the involvement of HIF pathway activation in the erythropoietic effects of Roxadustat. The oxidative stress correlations provide additional supportive evidence linking redox status with hematological recovery, while their lack of significant association with HIF-1α suggests that HIF stabilization and oxidative balance may not be directly coupled under the present experimental conditions.

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