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Review Article

Pentoxifylline Reno-Protective and Anti-Inflammatory Effects and Potential Role in Anemia of Chronic Kidney Disease

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ABSTRACT

Pentoxifylline (PTX), a methylxanthine phosphodiesterase inhibitor, is primarily known for its use in treating microcirculatory disorders due to its hemorheological effects. Pentoxifylline exhibits both anti-inflammatory and reno-protective effects via inhibiting important proinflammatory cytokines and interleukins including tumor necrosis factor- α (TNF-α), interferon-γ (IFN-γ) interleukin-1 (IL-1) and IL-6, and reducing oxidative stress. Progression of chronic kidney disease (CKD) is exacerbated by inflammation and oxidative stress, hence pentoxifylline can be a potential candidate to help ameliorate proteinuria in CKD patients, thereby slowing CKD progression and further decline in kidney function. In addition, pentoxifylline has beneficial effects concerning anemia which is a common complication in CKD patients because of erythropoietin deficiency, abnormalities in iron homeostasis, and inflammation-induced erythropoiesis suppression. Erythropoiesis stimulating agents (ESAs) are considered the standard treatment of anemia in CKD patients, but ESAs often encounter resistance primarily mediated by persistent inflammation. Hence the anti-inflammatory effects of pentoxifylline can help improve the responsiveness to ESAs, thereby improving hemoglobin levels and reducing ESA dose requirements. Consequently, pentoxifylline can help prevent poor cardiovascular outcomes and reduced quality of life, specifically in patients with end-stage renal disease (ESRD) on dialysis. The implications of these findings suggest that pentoxifylline could be a valuable addition to current treatment strategies, offering a comprehensive approach to the management of CKD and its associated anemia. This review emphasizes the mechanisms underlying the reno-protective and anti-inflammatory properties of pentoxifylline and explores the therapeutic potential of pentoxifylline in clinical practice.

Keywords: *Pentoxifylline; Proteinuria; Inflammation; Anemia; Chronic kidney disease*.

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1. Introduction

1.1. Pentoxifylline Background

Pentoxifylline is chemically classified as a xanthine derivative, similar to caffeine and theobromine. The Systematic name assigned by the International Union of Pure and Applied Chemistry (IUPAC) is 3,7-Dimethyl-1-(5-oxo-hexyl)-3,7-dihydro-purine-2,6-dione and its molecular formula is $C_{13}H_{18}N_4O_3$ **Fig. 1 [1, 2]**.

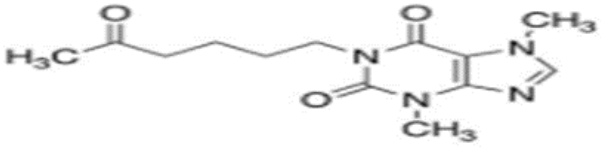

Fig. 1. Chemical structure of Pentoxifylline

Pentoxifylline was first registered in Germany and was approved for the management

of intermittent claudication in patients with chronic limb occlusive arterial disease. Pentoxifylline can improve blood flow by increasing the elasticity of both erythrocytes and leucocytes, preventing platelet aggregation, hence, pentoxifylline plays a pivotal role in whole blood viscosity. Also, pentoxifylline can induce vasodilation in addition to its anti-inflammatory and antioxidant properties **[3, 4]**. In addition, pentoxifylline has been used off-label for the treatment of some diseases including; peripartum cardiomyopathy, severe alcoholic liver disease, and non-alcoholic fatty liver disease due to the anti-fibrotic effects of pentoxifylline **[5]**.

2. Methodology

The methodology of this review article involved a comprehensive search of relevant literature using PubMed, Cochrane Library, and MEDLINE as the main databases. The search strategy was designed to identify studies that explore the reno-protective and anti-inflammatory effects of pentoxifylline, as well as its potential role in managing anemia in CKD. Keywords used in the search included "pentoxifylline," "chronic kidney disease," "anemia," "reno-protection," "anti-inflammatory," and "erythropoiesis-stimulating agents". The search was conducted without imposing time restrictions to ensure the inclusion of a broad range of research. Inclusion criteria focused on randomized controlled trials, cohort studies, and systematic reviews that specifically addressed the effects of pentoxifylline in adult CKD patients. Studies were selected based on their relevance to the topic, with a particular emphasis on those that provided detailed data on outcomes related to kidney function, inflammatory markers, and anemia management. Estimated glomerular filtration rate (eGFR), and proteinuria were selected diagnostic tools as they are widely recognized and utilized in clinical practice for assessing kidney function, making them suitable for evaluating the reno-protective effects of pentoxifylline **[6]**. Hemoglobin and hematocrit concentrations are widely recognized and utilized in the assessment of anemia, so they were the selected diagnostic tools used to evaluate the pentoxifylline effects on anemia in CKD patients **[7]**. Also, TNF-α, IL-6, and serum CRP levels were the diagnostic criteria used to assess inflammatory response to pentoxifylline therapy as they are commonly used parameters to evaluate inflammation **[8]**. The review also considered the quality of the studies, favoring those with well-designed and rigorously implemented research methods and larger sample sizes.

3. Pentoxifylline-an overview

3.1. Pharmacokinetics

Pentoxifylline is readily absorbed from the gastrointestinal tract and exhibits an oral bioavailability of around 20% to 30%. Pentoxifylline peak plasma concentration is achieved within 2 h. Once absorbed, pentoxifylline is metabolized into several active metabolites, with the primary metabolite being 1-(5-hydroxyphenyl)-3,7-dimethylxanthine (M-I, lisofylline), produced from pentoxifylline reduction in the liver and red blood cells (RBCs). M-I metabolite of pentoxifylline contributes significantly to its pharmacological effects. The half-life of pentoxifylline is approximately 0.4 to 1.6 h, but the half-lives of its metabolites can be longer, extending the drug's overall duration of action. Pentoxifylline is influenced by extensive first-pass metabolism in the liver, to overcome the frequent dosing obstacle, a pentoxifylline dosage form with sustained release (SR) properties was developed. The usual adult dose of pentoxifylline is 400 mg three times daily (TID) after meals, however, in patients with renal insufficiency, the dose has to be adjusted **[9, 10]**.

3.2. Mechanism of action

Pentoxifylline is a competitive nonselective phosphodiesterase (PDE) inhibitor that has an array of effects on inflammation by regulating the cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) intracellular levels through the improvement of cyclic nucleotide-dependent signal transduction and reduction of their hydrolysis **[11]**.

Many hypotheses regarding the pentoxifylline mechanism of action and its molecular and cellular actions are determined by studies on both humans and animals. Including pentoxifylline's hemorheological, anti-inflammatory, antioxidant, and immunomodulatory effects along with its impact on adhesion molecules and endothelial cells **[11]**.

3.2.1. Hemorheological effects

Pentoxifylline has hemorheological properties; and effects on blood cellular and flow properties, this could improve microcirculatory diseases, thus improving tissue perfusion. Pentoxifylline lowers blood viscosity by increasing leukocyte and erythrocyte elasticity and preventing platelets, and red and white cell aggregation. Furthermore, pentoxifylline can lower plasma fibrinogen levels and enhance the fibrinolytic activity of the plasma. Also, it could increase the intracellular levels of cAMP, inducing thromboxane synthesis inhibition and prostacyclin synthesis increase. Moreover, pentoxifylline reduces von Willebrand factor release and boosts the release of tissue plasminogen activator (tPA) **[12]**.

3.2.2. Immune modulation and Anti-inflammatory effects

The anti-inflammatory effects of pentoxifylline are due to the reduction in the production of the pro-inflammatory cytokines such as TNF-α and IFN-γ, also There is evidence to suggest that pentoxifylline influences IL-1 and IL-6 inflammatory cytokines, therefore pentoxifylline was studied for use in the treatment of a wide range of disease states with an inflammatory component. Inhibition of PDE in particular isozyme PDE-4 has a pivotal role in pentoxifylline anti-inflammatory effects as PDE-4 is highly expressed in inflammatory cells including neutrophils, macrophages, T cells, and endothelial cells, resulting in elevation of cAMP and its anti-inflammatory effects **[13, 14]**.

Pentoxifylline *possesses anti- -TNF-α properties* since it reduces TNF-α production; a key cytokine in the pathophysiology of various inflammatory disorders. Pentoxifylline inhibits the transcription of TNF gene, TNF messenger ribonucleic acid (mRNA) expression, and the release of TNF protein by macrophages and monocytes. The exact mechanisms by which pentoxifylline reduces the production of TNF-α remains unclear **[12, 15]**.

The intracellular cAMP levels modulate TNF-α synthesis by mononuclear phagocytes. The inhibition of PDE allows the second messenger cAMP to accumulate intracellularly which in turn results in protein kinase A (PKA) activation. After PKA activation, the transcription factor cAMP-response element binding protein (CREB) phosphorylation occurs, signals transmission to the nucleus, and gene transcription is modulated eventually. Also, high levels of intracellular cAMP lead to inhibition of the transcription of pro-inflammatory genes specifically the transcription of the TNF-α gene that is dependent on nuclear factor kappa light chain enhancer of activated B cells (NF-κB). Hence, pentoxifylline can lead to a reduction in the synthesis of pro-inflammatory cytokines and immune cell migration **[12]**.

Additionally, Pentoxifylline can suppress IFN-γ, IL-1,2,6,8 and 12 and monocyte chemoattractant protein (MCP) synthesis, Also, it

has been demonstrated that pentoxifylline can upregulate IL-10; an anti-inflammatory cytokine, in the monocytes. Peripheral blood mononuclear cells exhibit less IL-2 receptor when exposed to pentoxifylline. In addition, in cultured human keratinocytes, pentoxifylline inhibits the expression of IFN-γ inducible protein-10 (IP-10) mRNA. Pentoxifylline suppresses natural killer cell activity and causes inhibition of vascular cell adhesion protein-1 (VCAM)-1 and intercellular adhesion molecule-1 (ICAM)-1 expression. T and B lymphocyte activation can be inhibited by pentoxifylline through a cAMP-dependent pathway. Furthermore, pentoxifylline may prevent both T lymphocyte adhesion to keratinocytes and T cells, monocytes, and granulocyte adhesion to endothelial cells. Beyond influencing phagocytosis, It can reduce neutrophil aggregation and adhesion and prevent neutrophil degranulation and superoxide release **[16]**.

In vitro, pentoxifylline limits fibroblast proliferation and prevents the synthesis of intracellular and extracellular collagen by enhancing collagenase activity so collagen, glycosaminoglycans, and fibronectin levels decrease. Thus, pentoxifylline limits the formation of post-inflammatory fibrous tissue with subsequent limitation of post-inflammatory complications **[16]**.

Other anti-inflammatory effects are inhibitory effects on the phagocytic activity of human polymorph nuclear cells (PMNs) and monocytes resulting from increased intracellular levels of cAMP **[16, 17]**.

3.3. Pentoxifylline efficacy on the progression of CKD

The reno-protective and antiproteinuric effects of pentoxifylline have undergone a thorough review and meta-analysis recently. The majority of these analyses were dependent on clinical trials with different study designs and treatment approaches.

Some studies have demonstrated the importance of pentoxifylline to ameliorate inflammation and its consequences in chronic kidney disease patients. In the L González-Espinoza et al. study **[18]** on ESRD patients on hemodialysis, a significant decrease ($p<0.05$) in TNF-α levels in addition to other proinflammatory cytokines such as C- reactive protein (CRP), and IL-6, in the intervention group (18 patients who received pentoxifylline 400 mg daily) compared to the control group (18 patients received placebo for four months).

In Lin et al. study **[19]**, an open-label, randomized, controlled trial (RCT), 56 patients (72% of whom were nondiabetic) with stages 3 to 4 CKD and urinary protein excretion of more than 500 mg/g of creatinine, were assigned to either receive Angiotensin receptor blocker (ARB); losartan 100 mg daily for at least 6 months before enrollment, or ARB in addition to pentoxifylline; 400 mg once or twice daily depending on eGFR levels. When compared to the ARB group, the add-on pentoxifylline group had lower proteinuria at 12 months. Moreover, at 12 months the ARB group's eGFR had significantly decreased, while the add-on pentoxifylline group did not show a significant decrease in eGFR. In comparison to the ARB group, add-on pentoxifylline therapy decreased alterations in TNF-α and MCP-1 in urine. Then, after 1 year, the add-on pentoxifylline group's follow-up was continued while pentoxifylline was added to the ARB group. The findings of the study revealed that pentoxifylline treatment resulted in a consistent decrease in proteinuria, also the addition of pentoxifylline in the ARB for an additional 6 months follow-up, reproduced this benefit. Throughout the-18 month's follow-up period, pentoxifylline use was well tolerated by all patients. This was considered the first

instance where patients with stages 3 to 4 CKD would benefit from pentoxifylline addition to ARB for reduction of proteinuria.

The PREDIAN trial, an open-label, randomized controlled trial by Navarro-González et al **[20]**, encompassed 169 patients with type 2 Diabetes Mellitus, stages 3 to 4 CKD, and albuminuria of more than 30 mg/day, who underwent maximal renin-angiotensin-aldosterone system (RAAS) inhibition. The patients were randomized to either the control group (received RAAS blockers only) or to the pentoxifylline group (received 1200 mg of pentoxifylline daily in addition to similar doses of RAAS blockers) for a study duration of 24 months. The pentoxifylline group showed a less decline in eGFR and a higher reduction in albuminuria at the end of the study. The investigators concluded that in type 2 Diabetes Mellitus patients, the addition of 1200 mg of pentoxifylline daily to RAAS blockers resulted in a greater reduction of residual albuminuria after two years while a smaller decline in eGFR was observed. In the pentoxifylline group, it was proposed that these observations were linked to reduced TNF-α levels in urine.

Moreover, a single-center observational study by Chen et al **[21]**, including 609 stage 3B to 5 before ESRD, CKD patients were examined and revealed that pentoxifylline addition showed nephroprotection in the patients who had high proteinuria (≥1 g/gCr), indicating that proteinuria might serve as a predictor of pentoxifylline response for every individual patient.

Since the studies that focus on pentoxifylline administration in patients with advanced kidney disease and considering hard endpoints, such as doubling of serum creatinine, progression to ESRD, and mortality, are limited, Wu et al **[22]** study's purpose was to evaluate the reno-protective properties of pentoxifylline and its interaction with angiotensin-converting enzyme inhibitors (ACEI)/ARB, on ESRD and all-cause mortality in advanced CKD patients. The study analyzed a nationwide administrative dataset, and two propensity score-matched groups were identified, pentoxifylline users and nonusers. Each group included 7366 patients with advanced CKD, serum creatinine level > 6 mg/dL, received erythropoiesis-stimulating agents (ESAs), and non-dialysis dependent patients. Comparing patients who had received pentoxifylline to patients who had received RAAS blocker monotherapy, the authors observed that pentoxifylline users were protected from ESRD development and commencing dialysis. Moreover, it was found that in advanced CKD patients who are intolerant to RAAS blockers, the use of low doses of pentoxifylline; 200 mg daily, was effective to minimize the new onset ESRD risk.

The addition of pentoxifylline to RAAS blockers helped to decrease the risk for the composite outcome of long-term dialysis or death, as reported by Kuo et al **[23]** analysis of a dataset of advanced CKD patients. Although these cohort studies are observational, they represent the first proof that pentoxifylline can effectively reduce the risk of ESRD even among patients with late-stage CKD **[23]**.

On the other hand, an open-label, controlled trial observed 14 adult patients with insulin-dependent diabetes mellitus who also had nephrotic proteinuria. After one year, it was observed that no additive reno-protective or antiproteinuric benefits were evident from the addition of 400–800 mg pentoxifylline daily to ACEIs and ARBs. The limited sample size and non-randomization design of the study might have contributed to these unexpected findings. In addition, the abnormally high rate of creatinine clearance decline; >11 mL/min per year, raised concerns regarding the safety of dual RAAS blockers use **[24]**.

Likewise, the M Goicoechea et al. study **[25]** findings were that stages 3-5 CKD patients in the pentoxifylline group; who were treated with 800 mg daily had no significant decrease neither in the median urinary albumin excretion nor in the eGFR after 12 months (p= 0.000), whereas in the control group who continued their usual therapy, there was a worsening in eGFR by the end of the study (from 40.1±12.4 to 35.7±13.4 mL/ min per 1.73 m^2). Yet, proinflammatory cytokines; CRP, serum fibrinogen, and TNF-α that were measured at baseline, at 6 and 12 months of pentoxifylline treatment, showed a significant decrease at the end of the study in comparison to the control group (p= 0.002, p= 0.001 and p= 0.000, respectively).

3.3.1. Possible mechanisms underlying pentoxifylline's renal effects

The mechanisms underlying pentoxifylline's reno-protective activities are illustrated in **Fig. 2.** At first, pentoxifylline increases the intracellular cAMP levels through inhibition of PDE isozymes. Consequently, PKA activation occurs causing downstream effectors phosphorylation and inhibiting signaling pathways which trigger renal fibrosis and proteinuria. Hence, a novel treatment strategy for fibrotic kidney disease can be achieved through targeting PDE isozymes followed by intracellular cyclic nucleotide modulation **[26]**.

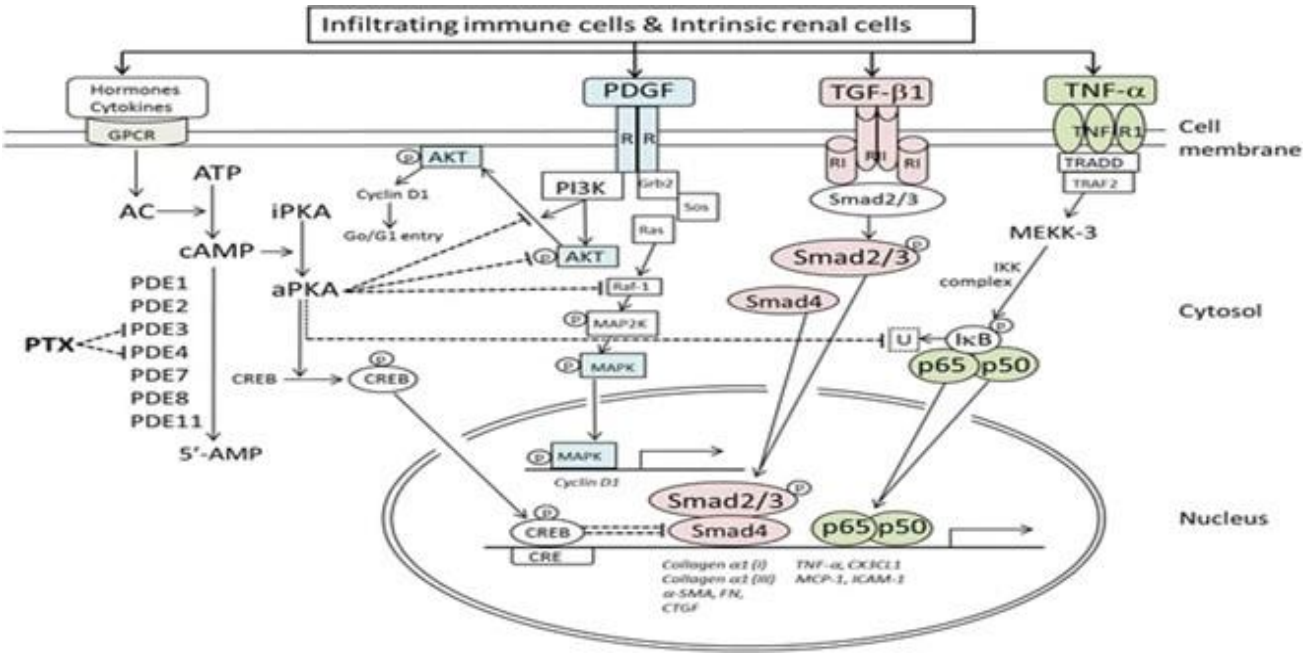

Fig. 2. Possible mechanisms mediating PTX's renal effects. AC, adenylate cyclase; aPKA, active protein kinase A; α-SMA, α-smooth muscle actin; ATP, adenosine triphosphate; cAMP, cyclic adenosine-3,5-monophosphate; CRE, cAMP response element; CREB, cAMP-response element binding protein; CTGF, connective tissue growth factor; CX3CL1, fractalkine; FN, fibronectin; GPCP, G-protein-coupled receptor; Grb2, growth factor receptor-bound protein 2; ICAM-1, intercellular adhesion molecule-1; IκB, inhibitory protein of NF-κB (p65/p50 heterodimer); IKK, IκB kinase; iPKA, inactive protein kinase A; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; P, phosphorylation; PDE, phosphodiesterase; PDGF, platelet-derived growth factor; PI3K, phosphatidylinositol 3-kinase; Sos, son of sevenless; TGF-β1, transforming growth factor-β1; TNF-α, tumor necrosis factor-α; PTX, pentoxifylline; TRADD, TNFR1-associated death domain protein; TRAF2, TNF receptor-associated factor 2; U, ubiquitination. Dash lines denote inhibitory pathways initiated by PTX from the leftmost side.

Following studies conducted in vitro, pentoxifylline inhibits PDE 3 and/or PDE 4 isozymes through a PKA-dependent mechanism, hence, cAMP levels increase but not cGMP.

While in studies that are conducted in vivo, pentoxifylline regulates the signaling pathways or components triggered by either cytokines such as TNF-α, NF-κB, ICAM-1, MCP-1, and CX3CL1 (fractalkine), or mitogens (platelet-derived growth factor, mitogen-activated protein kinase, phosphatidylinositol 3-kinase, protein kinase B (Akt) and cyclin D1) and fibrogenic molecules (transforming growth factor-β, Smad3/4, connective tissue growth factor, collagen 1 & 3, fibronectin and α-smooth muscle actin), this eventually leads to regeneration of the podocyte glomerular filtration barrier such as Wilms' tumor 1, nephrin, synaptopodin and podocin, reduced expression. Hence it can minimize proteinuria and renal pathology in non-diabetic kidney disease designs **[26-28]**. Pentoxifylline reduces renal hypertrophy, sodium retention, and albuminuria reduction as well as renal TNF-α, IL-1, and IL-6 levels in diabetic kidney disease (DKD) models. These findings reveal that irrespective of diabetes status, the renal effects of pentoxifylline might be mediated through proinflammatory cytokine cascade depletion **[29]**.

3.4. Erythropoiesis and kidney disease

3.4.1. Impact of inflammation on iron metabolism and erythropoiesis

3.4.1.1. Iron metabolism

Systemic immune activation results in the release of proinflammatory cytokines thus, anemia may be triggered or exacerbated due to prolonged inflammation through mechanisms that stimulate hepcidin production leading to iron trafficking abnormalities; including iron sequestration in macrophages and inhibition of dietary duodenal iron absorption. In addition, via a hepcidin-independent mechanism, TNF-α can directly decrease iron absorption in the duodenum. Iron restriction decreases heme synthesis and hemoglobin (Hb), as well as suppresses erythropoiesis through active iron-regulated erythroid mechanisms **[30, 31]**.

One prospective uncontrolled study and one randomized controlled trial reported improvement in transferrin saturation (TSAT) and total serum iron respectively, after pentoxifylline therapy, unlike other studies included in our review that did not record significant changes in iron parameters. Remarkably, an RCT on hemodialysis patients aimed to examine the impact of pentoxifylline treatment on serum hepcidin levels, the authors found that pentoxifylline had no significant impact on serum hepcidin levels. A pooled meta-analysis also revealed no significant differences in TSAT, ferritin, or total serum iron in patients treated with pentoxifylline as opposed to the standard therapy or placebo **[32-34]**.

3.4.1.2. Erythropoiesis

Erythropoiesis suppression in anemia of inflammation takes place because of reduced production or reduced biological activity of the erythropoietin hormone in the inflammatory state due to the suppressive actions of the proinflammatory cytokines including TNF-α and IL-1, on erythropoietin's hypoxia-mediated activation. The circulating levels of IL-1 and IL-6 are correlated negatively with the efficacy of erythropoietin-mediated signaling, highlighting the inflammation-driven hypo-responsiveness of erythropoietin receptors. Also, studies suggest that erythroid iron deficiency which develops in anemia of inflammation, results in the downregulation of erythropoietin receptors.

The erythropoietin's activity and availability

are decreased in anemia of inflammation and harms the induction of erythroferrone; hepcidin blockers, in turn, erythropoietin signaling is compromised and worsening hepcidin mediated erythroid iron restriction. Both iron restriction and the diminished effect of erythropoietin can impair erythroid cell proliferation and differentiation **[30]**.

3.4.1.3. Erythrocyte life span

The inflammatory state that has been linked to shortened erythrocyte lifespan, was attributed to factors including increased phagocytosis of the erythrocytes due to complement and antibody deposition on the erythrocytes, and activation of macrophages, also, the accumulation of fibrin in microvasculature that cause mechanical damage of the erythrocytes **[30]**.

3.4.2. Erythropoiesis stimulating agents (ESA) resistance as a consequence of anemia of inflammation in CKD patients

Anemia in CKD is often treated with ESAs, nonetheless one of the major contributors that is linked to ESA hypo-responsiveness in patients with CKD and ESRD is chronic inflammation. The greater inflammatory burden is correlated with higher ESA needs and non-erythropoietic effects of high ESA dose **[35]**.

In addition, many studies have indicated a correlation between erythropoietin resistance and increased levels of proinflammatory cytokines like TNF-α, IFN-γ, IL-1, and IL-6 in hemodialysis patients. In hemodialysis patients, high doses of ESA are linked to negative consequences including stroke, malignancy, and increased cardiovascular morbidity and mortality. Since pentoxifylline can reduce inflammation, it may improve the effectiveness of ESAs, thereby lowering the required dose of ESAs, therefore pentoxifylline might have therapeutic advantages in addition to cost savings **[36, 37]**.

3.4.3. Evidence supporting pentoxifylline in anemia treatment

Anemia in the case of CKD patients has a multifactorial nature, including deficiency of erythropoietin, chronic inflammatory status, iron metabolism abnormalities, and blood loss on hemodialysis; all comprise the most important etiologies **[38]**.

Anemia secondary to several disorders and inflammation is an important contributor to its development and progression. This is especially relevant to CKD as patients with CKD frequently suffer from a chronic inflammatory state which is related to various factors including higher incidence of infections, presence of arteriosclerosis, and increased levels of proinflammatory cytokines such as TNF-α, IL-1, IL-6, and serum CRP. Patients with uremia are persistently undergoing both immunosuppression and chronic immune system activation. Also, dialysis is associated with increased production of proinflammatory cytokines because of increased oxidant generation. Oxidative stress markers increase had been associated positively with CRP levels in hemodialysis patients. Pentoxifylline can help reduce the burden of inflammation-related anemia in CKD patients because of its anti-inflammatory properties. Poor anemia control in CKD is associated with worsening cardiovascular outcomes and reduced quality of life, particularly in dialysis patients **[39]**.

ESRD patients on dialysis have higher levels of inflammation in addition to the increased comorbidity; as a result, treatment of anemia in these patients is thought to be a more challenging target than in the CKD early stages. Since multiple evidences support that pentoxifylline administration may reduce proinflammatory cytokines specifically IFN-γ, TNF-α, IL-1, and IL-6 in hemodialysis and non-dialysis dependent patients, this anti-inflammatory effect may be translated into an improvement in hemoglobin

status and anemia control, thereby potentially reducing the need for blood transfusions and ESA dose **[40]**.

Some clinical trials have demonstrated a significant improvement in hemoglobin levels and reduced ESA dosage requirements when pentoxifylline is added to the treatment regimen for CKD-related anemia.

In 37 patients across three small, prospective uncontrolled investigations **[33, 41, 42]**, pentoxifylline had enhanced hemoglobin significantly from pre-treatment levels, the findings of these studies are summarized below as follows:

Pentoxifylline has been shown to have a positive impact on Hb levels in ESRD patients with anemia that is resistant to ESA, pentoxifylline treatment resulted in a significant increase in Hb levels. The mean hemoglobin levels in these patients increased from 9.5 g/dL to 11.7 g/dL after 4 months of 400 mg daily pentoxifylline therapy. These findings suggest a significant improvement in hemoglobin levels due to pentoxifylline effects on the inhibition of proinflammatory cytokines as the results showed a significant decrease in ex-vivo TNF-α expression in T cells from 58% to 31% after pentoxifylline treatment, accordingly erythropoiesis enhancement **[41]**.

The study by Ferrari et al **[33]** demonstrated that pentoxifylline therapy led to a significant elevation ($P<0.01$) in hemoglobin concentrations in stages 4–5 CKD patients. Specifically, the study showed that hemoglobin levels increased in 10 patients after the second week of pentoxifylline treatment and continued to rise, reaching 123 ± 6 g/L by week 4; the endpoint of the study. Furthermore, the improvement in hemoglobin levels observed with pentoxifylline treatment was associated with a significant reduction in circulating IL-6 levels, suggesting improved iron mobilization. Also, the study showed a positive association between serum ferritin and IL-6 levels, indicating the link between inflammation and iron metabolism in CKD patients **[33]**.

In AH Mohammadpour et al **[42]** study on ESRD patients with ESA-resistant anemia, hemoglobin levels were significantly increased in 8 patients (53% of patients) upon treatment with 400 mg pentoxifylline daily for 3 months. These findings were attributed to pentoxifylline anti-inflammatory properties, specifically reducing TNF-α cytokines, thus improving erythropoiesis and overcoming the hypo-responsiveness to ESA.

The Hero trial demonstrated that 26 patients who received 400 mg daily of pentoxifylline during a follow-up period of 4 months, had significantly increased Hb concentration by 7.6 g/L when compared to controls, however, pentoxifylline did not significantly modify ESA hypo-responsiveness, or ESA resistance index **[34]**.

Also, H Shahbazian et al **[43]** study concluded that the impact of 400 mg of pentoxifylline daily addition to ESA for six months in ESRD patients with ESA-resistant anemia was a significant increase in both hemoglobin and hematocrit levels; (9.33±1.25 g/dL and 28.08±3.88% at baseline; 11.22±1.26 g/dL and 34.02±3.72% respectively at the sixth month, $P= 0.01$). Another outcome of the study was a significant decrease in C-reactive protein levels within the group who received pentoxifylline in comparison to the control group. This reduction in CRP indicates the drug's effectiveness in controlling inflammation and improving response to ESA.

Another study by JF Navarro et al. study **[44]**, emphasized the impact of pentoxifylline on hemoglobin and hematocrit (HCT) in advanced renal failure patients who did not receive ESA,

and concluded that hemoglobin and hematocrit levels were increased significantly in the pentoxifylline group; 7 patients who treated with 400 mg daily for 6 month, compared to the control group (9.9±0.5 g/dL and 27.9±1.6% at baseline; versus 10.6±0.6 g/dL and 31.3±1.9%, respectively, $p<0.01$). Serum TNF- α concentrations were reduced significantly in the pentoxifylline group from 623±366 pg/mL; in the sixth month to 562±358 pg/mL: as opposed to the control group. Thus, the anti-cytokine properties of pentoxifylline improved the hematologic status in anemia patients.

JM Mora-Gutierrez et al **[45]** case-control observational study that retrospectively endorsed a significant increase in hemoglobin concentrations at three months and the end of the study ($P<0.001$) in 61.1% of hemodialysis patients who received 800 mg pentoxifylline daily which in turn lead to a reduction of the required ESA dose to maintain adequate hemoglobin levels in the pentoxifylline group after study completion ($P= 0.002$).On the contrary, the CRP levels were decreased in patients treated with pentoxifylline but the decrease was not significant compared to the control group, this may be attributed to sample size limitations.

On the contrary, the study by M Mortazavi et al **[46]** on ESRD patients on hemodialysis, where the patients in the pentoxifylline group (25 patients received 400 mg of pentoxifylline daily for 6 months in addition to ESA), did not show a significant change in hemoglobin concentrations, ferritin levels, or the dose of ESA when compared to the control group (25 patients received ESA and placebo). However, serum iron levels showed a significant increase in the pentoxifylline group. Thus, pentoxifylline may have a beneficial effect on serum iron levels.

3.4.4. Pentoxifylline safety and tolerability

Overall, pentoxifylline is administered orally and has a low incidence of serious side effects which makes it a well-tolerated more reasonable adjuvant therapy for the treatment of renal anemia and ESA hypo-responsiveness **[47]**.

The most common side effects include Gastrointestinal symptoms; dyspepsia, nausea, vomiting, bloating, and flatus: Central nervous system symptoms; headache, dizziness, anxiety, tremors, and confusion; and Cardiovascular symptoms; mild hypotension, angina, and chest pain **[34, 47, 48]**.

Contraindications

Pentoxifylline is contraindicated for patients with Known hypersensitivity to pentoxifylline or other methylxanthines like theophylline or caffeine. Patients who recently experienced retinal or cerebral hemorrhage should avoid pentoxifylline due to the increased risk of bleeding. Also, pentoxifylline should be avoided in case of pregnancy or breastfeeding **[49]**.

Limitations

In conducting this review, we aimed to provide a comprehensive overview however, some limitations were identified that may impact the generalizability of our conclusions. The heterogeneity among the studies, in terms of study design, patient populations, and outcome measures, posed challenges in synthesizing findings. Additionally, many of the included studies had short follow-up periods, which restricted our understanding of the long-term efficacy of pentoxifylline in CKD patients.

Conclusion

Apart from pentoxifylline's approved use in peripheral vascular disease, several studies suggest that pentoxifylline could be a valuable adjunct therapy in CKD patients. Pentoxifylline has shown both reno-protective effects that help to delay the progression of CKD as well as the

ability to manage anemia of inflammation and improve hemoglobin levels specifically in patients with ESRD who do not respond adequately to ESAs. Therefore, incorporating pentoxifylline into CKD treatment protocols may improve patient outcomes by addressing the complicated challenges associated with CKD. Large multicenter, long-term studies are recommended to confirm the beneficial effects of pentoxifylline.

List of abbreviations

ACEI, angiotensin converting enzyme inhibitors; Akt, protein kinase B; ARB, angiotensin receptor blocker; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CKD, chronic kidney disease; CREB, cAMP-response element binding protein; CRP, C- reactive protein; KD, Diabetic kidney disease; eGFR, estimated glomerular filtration rate; ESAs, Erythropoiesis stimulating agents; ESRD, end stage renal disease patients; Fig, Figure; g, gram; Hb, hemoglobin; HCT, hematocrit; ICAM-1, Intercellular Adhesion Molecule-1; IFN-γ, interferon-γ; IL-1, interleukin-1; IL-2, interleukin-2; IL-6, interleukin-6; IL-10, interleukin-10; IP-10, inducible protein-10; IUPAC, Systematic International Union of Pure and Applied Chemistry; MCP, monocyte chemoattractant protein; min, minute; mg, milligram; mL, milliliter; mRNA, messenger ribonucleic acid; NF-κB, nuclear factor kappa; PDE, phosphodiesterase; Pg, pictogram; PKA, protein kinase; PMNs, human polymorph nuclear cells; PTX, Pentoxifylline; RAAS, renin angiotensin aldosterone system; RBCs, red blood cells; RCT, randomized controlled trial; SR, sustained release; TID, three times daily; TNF-α, Tumor necrosis factor- α; tPA, tissue plasminogen activator; TSAT, transferrin saturation; VCAM-1, Vascular cell adhesion protein-1.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Publish

All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing Interests

The authors declare that no competing interests exist.

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Authors' Contributions

Study design, Radwa M. Elborolossy, Lamia M. El Wakeel, Radwa M. El Metwally, Magdy El Sharkawy. Data collection, Radwa M. El Metwally. Data interpretation and analysis, Radwa M. Elborolossy, Lamia M. El Wakeel, Radwa M. El Metwally, Magdy El Sharkawy. Drafting of manuscript, Radwa M. Elborolossy, Lamia M. El Wakeel, Radwa M. El Metwally, Magdy El Sharkawy.

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