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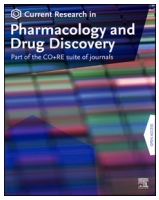

Alpha-lipoic acid: A promising pharmacotherapy seen through the lens of kidney diseases

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ABSTRACT

Kidney diseases have rapidly increased in prevalence over the past few decades, and have now become a major global public health concern. This has put economic burden on the public healthcare system and causing significant morbidity and mortality worldwide. Unfortunately, drugs currently in use for the management of kidney diseases have long-term major adverse effects that negatively impact the quality of life of these patients, hence making these drugs a "necessary evil". In recent times, antioxidant therapy has been explored as a potential pharmacological avenue for treatment of kidney diseases, and could offer a better therapeutic option with less adverse effect profile. One of such antioxidants is alpha-lipoic acid (ALA), a sulphur-containing multifunctional antioxidant that is endogenously produced by lipoic acid synthase in the mitochondria of many tissues, including the kidney. Burgeoning evidence indicates that ALA is showing clinical promise in the treatment and pharmacological management of many kidney diseases through its antioxidant and other therapeutic properties by activating several protective mechanisms while inhibiting deleterious signaling pathways. In this review, we present ALA as a potent naturally occurring antioxidant, its mitochondrial biosynthesis and pharmacological properties. In addition, we also discuss within the limit of present literature, ALA and its underlying molecular mechanisms implicated in experimental and clinical treatment of various kidney conditions, and thus, may offer nephrologists an additional and/or alternative avenue in the pharmacological management and treatment of kidney diseases while giving hope to these patients.

1. Introduction

Despite several decades of extensive research in nephrology and pharmacological management and treatment of kidney diseases, nephrologists are still faced with increased prevalence of kidney diseases, which has become a major public health concern worldwide (Carney, 2020; Ke et al., 2022; Kovesdy, 2011). This worrying trend has been projected to increase exponentially in the coming years due to a number of factors that are patient-specific, kidney- and drug-related, which promote various kidney diseases (Shahrbaf and Assadi, 2015; Luyckx et al., 2018). The kidneys play major roles in the body such as production of urine, vitamin D, erythropoietin, maintaining blood pH levels, and regulating fluid and electrolyte balance and blood pressure. As a metabolically active excretory organ, the kidneys are prone to a lot of harmful products such as iodinated contrast media, drug metabolites, xenobiotics with high nephrotoxic potential, infections and chronic diseases such as diabetes mellitus and hypertension (Cockwell and Fisher, 2020; Chen et al., 2020; Zhang et al., 2020; Shen et al., 2021; Gao et al., 2022, Engesser et al., 2024). Drugs such as everolimus and methotrexate are both used in transplantation as immunosuppressive agents and also in the management of some renal cancers. Biologics such as pembrolizumab, bevacizumab and ipilimumab are used as immunotherapy against renal cell carcinoma and more importantly, the possible use of ustekinumab in the management of antineutrophil cytoplasmic antibody-associated glomerulonephritis (ANCA-GM). (Stallmach et al., 2010; Porta et al., 2011; Chae et al., 2017). These drugs are expensive and present a lot of adverse effects, which reduce the quality of life of the patients. This development has led to the search for alternative

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compounds that have similar or superior renoprotective properties as that of the conventional medications but with less adverse effects. It must be pointed out that without appropriate, less toxic and economical access to nephroprotective agents, the burden on healthcare systems from patients with kidney diseases will skyrocket soon. The surge of kidney diseases are on the increase globally, with global annual figures for hospitalized patients with acute kidney disease standing at 13.3 million, out of which 11.3 million of these cases are in low-to middle-income countries (Francis et al., 2024). The risk of the development of chronic kidney disease (CKD) is generally higher in patients with a previous episode of acute kidney injury (AKI) than those with no history of AKI (Horne et al., 2017; Koh and Chung, 2024). CKD presents with an increase in strain on healthcare resources and also on kidney replacement therapies such as dialysis and transplantation in patients who go on to develop end-stage renal disease (ESRD).

Currently, a host of medications are being investigated for their potential renoprotective properties in an attempt to improve renal outcomes in patients worldwide. Drugs such as sodium-glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like-peptide 1 (GLP-1) agonists and inhibitors of renin-angiotensin-aldosterone system such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are among the most widely investigated in this regard. Recent studies have highlighted the renoprotective benefits of SGLT2i in preserving kidney function (Lin et al., 2021; Berezin and Berezina, 2024) aside its primary indication in lowering blood glucose levels mainly via glucosuria. Furthermore, the use of GLP-1 agonist in kidney diseases, particularly, diabetic nephropathy, has shown positive outcomes in reducing overall disease progression (Lin et al., 2023; Pan et al., 2024). On the contrary, Wajdlich and Nowicki (2024) reported that the use of liraglutide (an incretin mimetics for type 2 diabetic patients) in CKD patients increased blood pressure due to a decrease in natriuresis and increased aldosterone secretion, particularly in patients with estimated glomerular filtration rate of <30 ml/min/1.73 m^2.

Antioxidant therapy is emerging as an alternative primary or adjunct therapy in the management of some kidney diseases (Akkara and Sabina, 2020; Abo-Elmaaty et al., 2020; Uddin et al., 2021). One of such antioxidants that is receiving significant experimental and clinical attention in the treatment and pharmacological management of kidney diseases is alpha-lipoic acid (ALA). In this review, we present ALA as a potent naturally occurring antioxidant, its mitochondrial biosynthesis, and pharmacological properties. In addition, we also discuss within the limit of present literature, ALA and its underlying molecular mechanisms implicated in experimental and clinical treatment and management of kidney conditions such as AKI, CKD, ESRD, renal ischemia-reperfusion injury, diabetic nephropathy, hypertensive nephropathy, autosomal dominant polycystic kidney disease, and obstructive uropathy.

2. Alpha-lipoic acid

Alpha-lipoic acid (ALA), also known as thioctic acid, is a sulphur-containing natural antioxidant that scavenges free radicals in the body (Saboori et al., 2018; Skibska et al., 2023). Fruits and vegetables, as well as beef, kidney, and liver, are typical dietary sources of ALA (Basile et al., 2023). It is an essential cofactor in many cellular activities. ALA is a medium-chain fatty acid with sulphur atoms occurring at C6 and C8. The introduction of sulphur at C6 makes the carbon atom chiral. This chirality gives rise to two enantiomers or stereoisomers: R (+)-lipoic acid and S (−)-lipoic acid (Carlson et al., 2007). The S isomer is produced through a synthetic chemical reaction, while the R isomer naturally exists in food sources, particularly from meat and vegetables (Xu et al., 2023). Although -lipoic acid occurs naturally as the R-enantiomer, the synthetic supplement contains a racemic mixture of both R and S forms (Xu et al., 2023). The racemic mixture of ALA has recently been reported to be beneficial in the management of diabetic peripheral neuropathy (Verma, 2018), improvement of blood glucose and lipid profiles (Haghighatdoost and Hariri, 2019; Dugbartey et al., 2022a, 2022b, 2022c, Dugbartey et al., 2024), reduction of blood glucose levels and gamma-glutamyl transferase in pregnant women with gestational diabetes mellitus, management of irritable bowel disease in experimental models (Aslfalah et al., 2019), immunomodulation in autoimmune diseases such as systemic lupus erythematosus, chronic fatigue syndrome, liver disease, cardiovascular diseases as well as eye-related disorders such as glaucoma, cataract and retinal damage (Liu et al., 2019). The antioxidant property of ALA also suppresses various inflammatory pathways (Qiu et al., 2018; Dugbartey et al., 2022a, 2022b, 2022c; Skibska et al., 2023). ALA has also been demonstrated to inhibit the progression of breast cancer in experimental models by inactivating transforming growth factor-beta (TGF-β) (Tripathy et al., 2018). ALA has also been recently reported to exhibit neuroprotective and neurorestorative effects through its antioxidant property (Kulikova et al., 2018). In fact, ALA administration (20 mg/kg) through the jugular vein resulted in neuroprotection by decreasing mortality, neurological deficit score, infarction, and increasing neurogenesis and brain cell metabolism (Choi et al., 2015).

ALA is readily absorbed from the gastrointestinal tract with a mean plasma half-life of 30 min and a mean bioavailability of 30%. The pH-dependent cellular uptake of ALA is mediated by sodium-dependent multivitamin transporter (SMVT) and monocarboxylate transporter (Waslo et al., 2019). SMVT is highly specific to the *R* enantiomer of ALA, and the bioavailability of the *R* enantiomer is almost two-fold higher than the *S* form (Huerta et al., 2019). The pharmacokinetic parameters of R (+)-ALA are relatively better than that of S (+)-ALA. Therefore, the R-enantiomer has been suggested to be given in more quantities than in a racemic mixture form (Uchida et al., 2015). Also, the R-enantiomer of ALA has been shown to be a rather potent antioxidant *in vivo* compared to the racemic mixture of ALA (Yoon et al., 2016). Oxidative decarboxylation of pyruvate (a step where ALA, together with pyruvate dehydrogenase decarboxylates pyruvate to acetyl CoA) and α-ketoglutarate (a step where ALA, along with α-ketoglutarate dehydrogenase decarboxylates α-ketoglutarate to succinyl CoA in the citric acid cycle) are examples of the many of biological activities involving ALA (Ramachanderan, 2019).

ALA chelates heavy metal ions such as iron, copper and zinc, thereby reducing ROS by interfering with the Fenton and Haber-Weiss reaction (Saboori et al., 2018; Camiolo et al., 2019). ALA also increases the expression of other naturally occurring antioxidant enzymes such as catalase (for the conversion of hydrogen peroxide to water and oxygen), superoxide dismutase (SOD), both copper/zinc-SOD, located in the cytosol of eukaryotic cells and manganese-SOD, found in the mitochondria of eukaryotic and some bacteria - for the conversion of superoxide ions to either hydrogen peroxide or molecular oxygen (Moeinian et al., 2019). Also, ALA bolsters the expression of glutathione peroxidase (GPx) (for reduction of lipid hydroperoxides to their corresponding alcohols, as well as reduction of hydrogen peroxide to water), and also restores antioxidants such as vitamins C (ascorbic acid), E (α-tocopherol) and glutathione (GSH) (Moeinian et al., 2019).

3. ALA for the treatment and management of kidney conditions

ALA is emerging as a potent drug with renoprotective properties that could provide additional and/or alternative avenue in the pharmacological management and treatment of kidney diseases. The mechanisms underlying the potential renoprotective action of ALA include suppression of vasoconstriction system (e.g. endothelin pathway) while activating vasodilatory system and restoring antioxidant, anti-inflammatory and anti-apoptotic pathways.

3.1. ALA for toxic nephropathies

Acute kidney injury (AKI) is prevalent particularly in patients receiving certain anti-cancer drugs and antibiotics (Kang et al., 2009). Cytotoxic drugs such as cisplatin, methotrexate and doxorubicin and

antibiotics such as gentamycin and neomycin are regularly used in treatment regimens globally. In a rat model of cisplatin-induced AKI, intraperitoneal administration of 50 mg/kg of ALA on days 2 and 1, and 8 h prior to 6 mg/kg cisplatin administration, followed by injection on days 1, 2 and 3 after cisplatin administration resulted in increased renal expression of aquaporins 1–3, improved urine concentration and tubular sodium reabsorption, with increased renal expression of adenylyl cyclase VI and vasopressin-induced cAMP production, and partly contributed to prevention of cisplatin-induced AKI (Bae et al., 2007, 2009). These effects were reversed in cisplatin-treated rats without ALA administration Specifically, the increased expression of aquaporins 1–3 by ALA were localized in the cortical and medullary regions of the kidney as revealed by semi-quantitative immunoblotting and immunohistochemical staining (Bae et al., 2007, 2009). This result was confirmed in another study in which intraperitoneal administration of 50 mg/kg of ALA preserved renal expression of aquaporin 2 and Na^+/H^+ exchanger, which were significantly downregulated by lipopolysaccharide (LPS), and partly contributed to attenuating LPS-induced AKI in rats (Suh et al., 2015). In addition, prophylactic treatment with 100 mg/kg/day ALA for 30 days improved renal function parameters such as serum creatinine and blood urea nitrogen (BUN) and prevented cisplatin-induced AKI in rats (Khalifa et al., 2020). Kang et al. (2009) also observed downregulation and reduced production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and adhesion markers such as intercellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), as well as inhibition of the activation of the inflammation-related transcription factor, nuclear factor kappaB (NF-κβ) following 100 mg/kg administration of ALA in a mouse model of cisplatin-induced AKI. Furthermore, intraperitoneal administration of 10 mg/kg of ALA also improved renal levels of antioxidant enzymes such as SOD, CAT and glutathione, reduced renal levels of malondialdehyde (MDA; a by-product of lipid peroxidation and indicator of reactive oxygen species [ROS] production), and thus partly contributed to attenuating cisplatin-induced AKI in rats (Adikwu et al., 2019) and also preserved renal structure (Fig. 1). The administration of ALA in experimental animals with AKI induced by drugs such as doxorubicin, methotrexate, gentamycin and vancomycin, produced results similar to that in cisplatin-induced nephrotoxicity, with the similar mechanisms of protection (Sandhya et al., 1995; Malarkodi et al., 2003; Celik et al., 2005; Armagan et al., 2015; El-Sayed et al., 2017; Darwish and El-lateef, 2018; Adikwu et al., 2019). These observations highlight the potential renoprotective effect that ALA could exhibit when used as a primary and/or adjuvant therapy in patients receiving nephrotoxic medications.

AKI is also seen in patients undergoing coronary angiography and percutaneous intervention, which rely on the use of iodinated contrast media for diagnostic radiographic imaging of the coronary arteries. This radiographic procedure involves administration of intravascular iodinated contrast media, which unfortunately induces AKI as a complication of the procedure. Contrast-induced AKI (CI-AKI) occurs in about 30% of patients receiving intravenous contrast media, and is currently the third most common cause of hospital-acquired AKI next to renal hypoperfusion and post-operative renal injury (Fähling et al., 2017; Tanık et al., 2019). The use of ALA has been investigated in human and animal models of CI-AKI with varying success. Not a great deal of research has been carried out in this area. However, the results obtained from the few available studies do not appear to support the use of ALA in the prevention of CI-AKI. For example, a prospective randomized controlled trial by Jo et al. (2013) concluded that the use of ALA as a prophylactic agent in patients receiving contrast media did not offer any superior protection to that of placebo. Another clinical study involving diabetic patients undergoing coronary angiography demonstrated that ALA did not decrease the risk of CI-AKI in this subset of diabetic patients (Cicek et al., 2013). However, other antioxidants such as N-acetyl cysteine, vitamin C, and vitamin E were reported to significantly reduce CI-AKI in 49 human clinical trials (Ali-Hasan-Al-Saegh et al., 2017). While the clinical trials involving ALA did not explain why ALA did not reduce the incidence of CI-AKI, it is possible that the study protocol may have

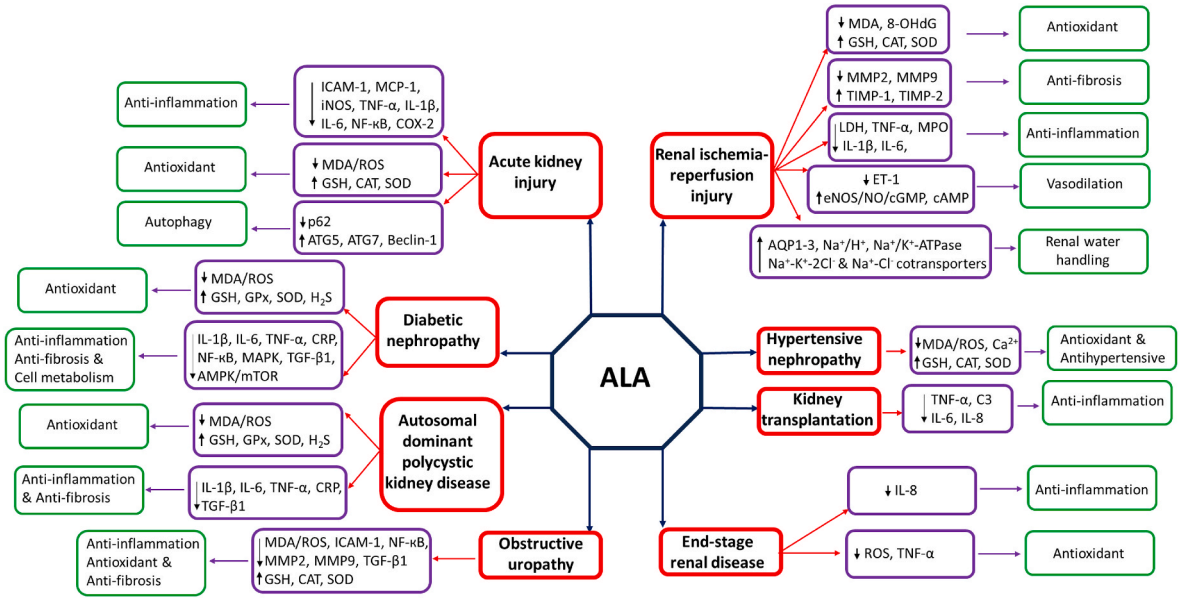

Fig. 1. Mechanisms of renal protection by alpha-lipoic acid in kidney diseases. ALA: Alpha-lipoic acid; AQP1-3: Aquaporins 1–3, LDH: Lactate dehydrogenase, Intercellular adhesion molecule-1, MCP-1: Monocyte chemoattractant protein-1, iNOS: Inducible nitric oxide synthase, eNOS: Endothelial nitric oxide synthase, TNF-α: Tumor necrosis factor-alpha, IL-1β: Inerleukin-1beta, IL-6: Interleukin-6, IL-8: Interleukin-8, NF-κB: Nuclear factor kappaB, MAPK: Mitogen-activated protein kinase, COX-2: Cyclooxygenase-2, MDA: Malondialdehyde, ROS: Reactive oxygen species, GSH: Glutathione, GPx: Glutathione peroxidase, CAT: Catalase, SOD: Superoxide dismutase, ATG5:Autophagy related 5, ATG7: Autophagy Related 7, MMP-2: Matrix metalloproteinase-2, MMP-9: Matrix metalloproteinase-9, TIMP-1: Tissue inhibitor of metalloproteinase-1, TIMP-2: Tissue inhibitor of metalloproteinase-2, TGF-β1: Transforming growth factor-beta1, ET-1: Endothelin-1, NO: Nitric oxide, cAMP: Cyclic adenosine monophosphate, cGMP: Cyclic guanosine monophosphate, AMPK: AMP-activated protein kinase, mTOR: Mammalian target of rapamycin, 8-OHdG: 8-hydroxy-2′ -deoxyguanosine, MPO: Myeloperoxidase, CRP: C-reactive protein, H_2S: Hydrogen sulfide, Ca^{2+}: Calcium ion, and C3: Complement component 3.

significantly impacted the study outcome, as ALA (600 mg) was administered only 2 days before and after coronary catheterization. Perhaps a higher dose and longer treatment duration may decrease CI-AKI development. Taken together, ALA administration protects against many forms of AKI.

Colistin, an antibacterial agent used in the management of multi-drug resistant infections, is notoriously known to have nephrotoxicity as one of its main adverse effects (Mosayebi et al., 2021). ALA has shown promise in the attenuation of nephrotoxicity induced by colistin administration (Oktan et al., 2021), highlighting the diverse roles that ALA plays in disease prevention and/or management. In this study, ALA pre-treatment reduced kidney damage (decrease urine KIM-1 levels, MDA, caspase-3 and urine albumin/creatinine ratio). Ferroptosis has recently been described as a key driver in the development of kidney diseases. It is a form of cell-death mediated in part by accumulation of iron, abnormal amino acid metabolism and subsequently, increased reactive oxygen species production via lipid peroxidation (Zhang and Li, 2022; Li et al., 2023). ALA has been shown to ameliorate the effects of iron in an experimental rat model where there was a reduction in mRNA levels of Nox4, p22phox, TNF-α and KIM-1 (Cavdar et al., 2020).

3.2. ALA for renal ischemia-reperfusion injury and sepsis

Ischemia-reperfusion injury (IRI) refers to tissue injury caused by temporary cessation of blood supply to a tissue and subsequent restoration of blood supply to the ischemic tissue. This is a "hot" area that has attracted significant scientific attention, especially among nephrologists and kidney transplant surgeons, as it is an inexorable problem in transplantation of kidney and other transplantable organs. In a rat model of renal IRI, which was induced by 1-h occlusion of the left renal pedicle followed by a 6-h period of reperfusion, intraperitoneal administration of 100 mg/kg of ALA at 30 min prior to induction of ischemia reduced the levels of renal ROS and the fibrotic proteins, matrix metalloproteinase 2 (MMP2) and MMP9, which were significantly elevated during ischemia and reperfusion (IR) (Cavdar et al., 2014). It is important to note that MMPs are involved in pathological remodeling of renal tissue, which is associated with renal dysfunction (Rodríguez-Sánchez et al., 2019). In addition, ALA administration markedly increased renal expression of tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 proteins as well as renal GSH (Cavdar et al., 2014). These changes mediated by ALA, ultimately resulted in reduced serum creatinine and preserved renal ultrastructure, and thereby culminating in renal protection (Cavdar et al., 2014). This promising result supports that of a previous study by Takaoka et al. (2002) in which rats were subjected to 45 min of ischemia by occluding sthe left renal artery and vein followed by reperfusion, 14 days after contralateral nephrectomy. In this study, both glomerular and tubular function significantly decreased 24 h following reperfusion evidenced by abnormally increased levels of serum creatinine, BUN and decreased creatinine clearance and urinary osmolality, with severe renal lesions upon histopathological examination. Conversely, intraperitoneal administration of 10 mg/kg of ALA prior to induction of ischemia prevented this pathological alteration and improved renal dysfunction (Takaoka et al., 2002). Interestingly, a higher of ALA (100 mg/kg) produced a better renal production than the lower dose (10 mg/kg) as seen in significantly lower tubular necrosis score, and fewer proteinaceous casts in tubuli and congestion in the renal medulla. Mechanistically, ALA strongly downregulated renal expression of endothelin-1 (ET-1), which was markedly upregulated after IR (Takaoka et al., 2002). ET-1 is a potent vasoconstrictor peptide produced by vascular endothelial cells, which in turn, activates several pathological factors such as NF-κB and TNF-α and contributes to oxidative stress-mediated endothelial dysfunction (Zhang and Frei, 2001; Bhatt et al., 2014). The inhibitory effect of ALA on ET-1 has been shown in preclinical and clinical investigations in which ALA suppressed vascular overproduction of ET-1 and activated the pathway that synthesizes nitric oxide (NO; a potent vasodilator whose vasodilatory action is via eNOS/NO/cGMP pathway) (Heitzer et al., 2001; Takaoka et al., 2001; Ahmad et al., 2018) (Fig. 1). As such, ALA administration was found to attenuate the loss of eNOS phosphorylation in diabetic patients and animals, and thus improved endothelial function (Heitzer et al., 2001; Sena et al., 2008). Along this line of evidence, Bae et al. (2008) observed that intraperitoneal administration of 80 mg/kg of ALA before and immediately after 40 min occlusion of renal pedicles of rats significantly downregulated renal mRNA expression of ET-1 to control level, which was strongly upregulated by IR. In the same study, induction of IR markedly decreased eNOS expression, cGMP and cAMP generation and downregulated the expression of aquaporins 1–3 as well as sodium transporters such as Na^+/K^+-ATPase, type 3 Na^+/H^+ exchanger, Na^+-K^+-$2Cl^-$ cotransporter, and Na^+-Cl^- cotransporter. Remarkably, ALA significantly prevented the decreased expression of eNOS, stimulated cGMP and cAMP production, and strongly upregulated expression of aquaporins 1–3 and sodium transporters (Bae et al., 2008) (Fig. 1).

Another model of IRI also showed that 45 min of renal pedicle occlusion followed by 24 h of reperfusion in unilaterally nephrectomized rats induced substantial increases in serum creatinine, BUN, IL-1β, IL-6, TNF-α, MDA, activity of myeloperoxidase (MPO, neutrophil marker), as well as increases in lactate dehydrogenase (LDH; a marker of cell and tissue damage), 8-hydroxy-2′-deoxyguanosine (8-OHdG; a marker of oxidative DNA damage) and collagen deposition, which corresponded with decreases in GSH, total antioxidant capacity and Na^+/K^+-ATPase activity. However, intraperitoneal injection of ALA (100 mg/kg) at 15 min before induction of ischemia and just before reperfusion reversed these biochemical parameters and the pathological changes in the kidney and improved renal integrity (Sehirli et al., 2008) (Fig. 1). This result indicate that ALA protects against renal IRI through its antioxidant, anti-inflammatory and other therapeutic properties. The same salutary effect was observed in very recent studies when rats received daily prophylactic treatment with 50 mg/kg of ALA (intraperitoneally) for 2 weeks prior to induction of IRI (Ahmadvand and Mahdavifard, 2019) as well as with ALA derivatives and under condition of renal damage induced by limb IRI (Koga et al., 2012; Othman et al., 2022). Collectively, these experimental findings demonstrate that renal protection by ALA against IRI is partly due to inhibition of vasoconstrictive mechanisms while simultaneously activating vasodilatory pathways and improving tubular transport function as well as other potentially protective but unidentified mechanisms.

Another form of AKI is sepsis-induced AKI. Sepsis is a life-threatening dysregulated systemic response to bacterial infection. Although it can cause multiorgan failure, the kidney is the most affected organ (Li et al., 2014). Unfortunately, effective pharmacotherapy for sepsis-induced AKI is lacking, suggesting the need to identify or develop pharmacological agents for this condition. ALA supplementation has been studied in experimental models of sepsis. In these studies, the authors reported preservation of renal integrity following ALA administration, which corresponded with increase in antioxidant enzymes and a decline in MDA and protein carbonyl (Suh et al., 2015; Petronilho et al., 2016). A recent study also showed that ALA protects against sepsis-induced AKI in rats by promoting autophagy as seen in increased LC3II/I ratio (autophagy marker), upregulated renal expression of the autophagy factors, ATG5 and ATG7, as well as beclin-1 (autophagy and anti-apoptotic protein) and downregulated renal expression of p62 protein (an autophagy protein that promotes NF-κB activation), and thereby facilitating autophagosome accumulation in the septic kidney (Jia et al., 2019). This changes at the molecular level resulted in reduced levels of BUN and serum creatinine, which corresponded with improved renal ultrastructure and survival rate of septic rats (Jia et al., 2019). Other studies also the protective action of ALA against sepsis-induced AKI to its anti-inflammatory property by inhibiting NF-κB signaling pathway and suppressing the release of pro-inflammatory cytokines such as TNF-α, iNOS, interleukin-1beta (IL-1β) and IL-6 in septic kidneys (Li et al., 2014, 2015) (Fig. 1). ALA has also been identified to ameliorate

mitochondrial oxidative stress, and preserved type 3 Na^+/H^+ exchanger and aquaporin 2 expression in septic kidneys of rats (Suh et al., 2015). In addition, ALA reduced ROS-mediated kidney injury by suppressing the production and release of cyclooxygenase-2 (COX-2; a pro-inflammatory enzyme) and inducible nitric oxide synthase (iNOS; a pro-inflammatory mediator) in cultured mesangial cells (Li et al., 2015).

3.3. ALA for diabetic nephropathy

Diabetic nephropathy (DN) is one of the major microvascular complications of diabetes mellitus. It is seen in both type 1 (T1DM) and type 2 diabetes mellitus (T2DM) but more common in the latter than the former because of the high prevalence of the latter than the former. DN is a clinical syndrome characterised by albuminuria (>300 mg/day or >200 μg/min) confirmed on at least two occasions 3–6 months apart, permanent and irreversible decrease in glomerular filtration rate due to angiopathy of glomerular capillaries (Adler et al., 2003). It is currently the leading cause of end-stage renal disease (ESRD) for which renal replacement therapy, such as dialysis or transplantation is required (Gnudi et al., 2016; Dugbartey, 2017). It presents with a myriad of pathophysiological changes hyperglycemia-induced ROS production, which ultimately lead to glomerulosclerosis, tubulointerstitial fibrosis and vascular remodeling (Hayden et al., 2005; Reiniger et al., 2010). DN results in a cascade of hemodynamic events such as increased intraglomerular and systemic pressure, increased expression of ET-1, vascular endothelial growth factor and suppressed production and release of nitric oxide and endogenous antioxidants such as catalase, glutathione, SOD and GPx (Kalani, 2008; Satirapoj and Adler, 2014).

Growing evidence from human and animal studies shows that administration of ALA is protective against DN development and progression. In a randomized control trial involving 34 patients with DN, oral administration of ALA (800 mg/day) with pyridoxine (80 mg/day) for 12 weeks resulted in significant decrease in advanced glycation end-products, albuminuria and systolic blood pressure, and improved antioxidant and glycemic status, along with increased serum nitric oxide compared to placebo-treated control group (Noori et al., 2013). The same salutary effect was observed in other randomized controlled trials with more than 60 DN patients in which ALA was administered for 2–8 weeks (Sun et al., 2017; Hong et al., 2017; Qu et al., 2018; Cao and Chen, 2021). Lipoic acid synthetase (LAS) is an enzyme responsible for the synthesis of ALA in the body. A recent clinical study revealed a reduced level of LAS in DN patients (Esawy and Magdy, 2020), suggesting that LAS could represent a useful biomarker for the diagnosis of DN and perhaps other diabetic complications. In support of this clinical observation, a genetic study showed acceleration of DN, with increased ROS-induced oxidative stress in T1DM mice that lack LAS gene (Yi et al., 2012). In another clinical study the effect of ALA on vascular smooth muscles was investigated in 101 T2DM patients, administration of ALA (0.6 g/day) in addition to conventional hypoglycemic therapy for 2 weeks, significantly attenuated dysfunctional vascular smooth muscle by increasing the production of hydrogen sulphide (H_2S) when compared to non-diabetic control group (n = 20) that was age- and sex-matched (Qiu et al., 2018). In a separate study by the same authors, intraperitoneal daily administration of ALA (100 mg/kg) for 8 weeks to streptozotocin-treated T2DM rats upregulated the expression of cystathionine γ-lyase (CSE; H_2S-producing enzyme), increased serum H_2S level, prevented hyperglycemia and inhibited autophagy in vascular smooth muscle cells via AMPK/mTOR pathway (Qiu et al., 2018). These preclinical and clinical observations align with the results of our recent studies in which oral daily administration of ALA (60 mg/kg) to streptozotocin-induced T2DM rats with or without conventional hypoglycemic therapy for 6 weeks, activated renal H_2S system, restored normoglycemia, and prevented ROS-induced renal damage in a rat model of DN (Dugbartey et al., 2022a, 2022b). H_2S is an endogenously produced gaseous signaling molecule that is involved in cellular homeostasis at low physiological concentrations, and has been reported to exhibit protection against several renal pathologies and other metabolic conditions through diverse molecular mechanisms (Ahangarpour et al., 2014; Feng et al., 2015; Huang et al., 2016; Dugbartey et al., 2022c, 2022d, 2022e).

In other rodent models of DN, administration of ALA to diabetic rats prevented podocyte loss, reversed hyperglycemia, and reduced serum levels of advanced glycated end-products, IL-6, TNF-α, MDA, and c-reactive protein (CRP) and other markers of renal injury (Obrosova et al., 2003; Siu et al., 2006; Wang et al., 2013). These changes corresponded with increased activities of antioxidant enzymes such as SOD and GPx in diabetic kidneys (Obrosova et al., 2003; Bhatti et al., 2005; Wang et al., 2013). In addition, ALA administration prevented collapse of mitochondrial membrane potential, attenuated Ca^{2+}-induced mitochondrial swelling and voltage-gated anion channel signal decrease in kidneys of diabetic rats (Wang et al., 2013). These empirical findings highlight the anti-inflammatory and antioxidant action of ALA as well as its ability to preserve mitochondrial integrity while restoring normoglycemia under diabetic condition. In another rat model of DN, ALA administration for 5 weeks attenuated proteinuria by downregulating renal cortical expression of fibrotic markers, transforming growth factor-beta1 (TGF-β1) and fibronectin, via inhibition of p38 MAPK signaling pathway (Lee et al., 2009), and inhibited proliferation of high glucose-exposed human mesangial cells via the same mechanism (Zhang et al., 2021) (Fig. 1). Taken together, ALA offers therapeutic benefit in clinical and preclinical models of DN.

3.4. ALA for hypertensive nephropathy

In addition to the protective role of ALA in the renal pathologies discussed in the preceding sections, ALA has also been reported to prevent the pathogenesis and progression of hypertensive nephropathy in experimental models (Midaoui et al., 2003; Louhelainen et al., 2006), with increased free sulfhydryl groups of membrane Ca^{2+} channels, leading to normalisation of intracellular Ca^{2+} concentration, vascular resistance and blood pressure (Vasdev et al., 2005). In a rat model to investigate the effect of ALA on hypertensive nephropathy, ALA increased the production of renal antioxidants such as CAT, GSH and SOD while decreasing the levels of MDA, protein carbonyls, urinary creatinine and proteinuria (Chandran and Sirajudeen, 2019) as well as increase in baroreflex sensitivity in hypertensive rats (Queiroz et al., 2012) (Fig. 1). Remarkably, ALA treatment also prevented thickening and narrowing of the lumina of small arteries, the development of necrosis in the glomeruli and a mild hyperplasia of smooth muscles of an experimental model of hypertension (Vasdev et al., 2003). The diminished production of renal and vascular ET-1 may account for the protective effect of ALA in preserving renal and vascular function from ROS- and hypertension-mediated damage (Takaoka et al., 2001; Louhelainen et al., 2006). Clinical studies also confirmed data obtained from murine studies about the beneficial role of ALA in protecting blood vessels from ROS-mediated damage and dysfunction, a situation which prevents the development of renovascular hypertension and damage (Hajizadeh-Sharafabad and Sharifi Zahabi, 2022; Rahman et al., 2012). In addition, ALA supplementation prevented glomerular and vascular damage in spontaneous hypertensive rats, with significant improvement in creatinine clearance and proteinuria, increased N-acetyl-(D)-glucosaminidase activity (Martinelli et al., 2021), and improved blood pressure level via a reduction in cytosolic free calcium level and oxidative stress (Midaoui and de Champlain, 2002; Vasdev et al., 2003). In summary, these empirical findings suggest that ALA may serve as pharmacological tool for the treatment of hypertension and hypertensive nephropathy, and potentially other hypertensive complications.

3.5. ALA for end-stage renal disease

During hemodialysis, there is activation of immune cells, particularly leukocytes on the surface membrane of the dialyzer, leading to the

generation of ROS, one major unwanted side effect associated with patients undergoing hemodialysis. High concentrations of accumulated pro-inflammatory and pro-oxidant toxins also initiate an inflammatory response that ultimately lead to the production of ROS (Ninic et al., 2018; Kohlová et al., 2020). To mitigate this unwanted side effect, emerging studies show that treatment of polysulfone membranes with ALA for dialysis reduced ROS production, decreased platelet adhesion and activation, with the membranes maintaining their ability for selective separation of biomolecules (Mahlicli and Altinkaya, 2014; Kohlová et al., 2020). A study by Ahmadi et al. (2013) highlighted the usefulness of a combination of ALA and vitamin E in reducing oxidative stress and inflammatory markers in hemodialysis patients. Also, ALA markedly reduced serum levels of pro-inflammatory cytokines (IL-8 and TNF-α) in a double-blinded randomized clinical trial in ESRD patients undergoing hemodialysis (Safa et al., 2014) (Fig. 1). ALA has also been reported to be beneficial as an erythropoietin adjuvant in ESRD patients undergoing hemodialysis (El-Nakib et al., 2013). These clinical reports show that ALA could be a potential drug of choice for ESRD patients undergoing hemodialysis therapy.

3.6. ALA in kidney transplantation

Kidney transplantation is a routine life-saving procedure for ESRD patients. It offers improved quality of life and significant survival advantage at a cheaper cost compared to dialysis therapy. However, transplant-induced IRI increases the incidence of delayed graft function (DGF), primary non-function, graft rejection and other post-transplant complications, and thereby hampering the short- and long-term success of kidney transplantation. Emerging clinical evidence shows that ALA administration results in beneficial outcome after kidney transplantation. In a clinical trial involving 26 patients undergoing simultaneous kidney-pancreas transplant, the effect of ALA was evaluated through functional recovery of the renal graft as well as biochemical markers of IRI (Ambrosi et al., 2016). In this clinical study, administration of 600 mg of ALA to deceased donors at the time of donor kidney procurement and to recipients immediately before the surgical procedure resulted in significantly reduced renal expression of TNF-α and C3 (a protein in the complement system) and serum IL-8, IL-6, lipase and amylase secretory leukocyte protease inhibitor, and mediated early kidney function compared to untreated control recipients (Ambrosi et al., 2016) (Fig. 1). This positive clinical outcome highlights the anti-inflammatory action of ALA, showing that ALA contributes to attenuating transplant-induced IRI and improves renal graft function after transplantation. A similar result was presented at the American Transplant Congress in 2013 when Guerrieri et al. (2013) observed in another clinical trial involving 18 patients recruited for kidney-pancreas transplantation in which intravenous administration of 600 mg of ALA to deceased donors at the time of renal graft retrieval and to the recipients during the surgical procedure. In a clinical trial, administration of 2600 mg of ALA to 18 patients just before kidney transplantation along with perfusion of the renal grafts with 600 mg of ALA 1 h before transplantation markedly reduced plasma creatinine level and severity of DGF, and prevented renal allograft rejection while increasing MDRD during the first 14 days after kidney transplantation compared to placebo-treated control group (18 patients) (Weber et al., 2017). Although ALA did not prevent the occurrence of DGF in this study, it improved renal graft function, and prevented early rejection episodes and a return to dialysis after transplantation. Using the same protocol, this observation was confirmed by Osella et al. (2019) who also reported markedly lower levels of plasma creatinine and BUN and higher MDRD in 31 ALA-treated kidney transplant recipients compared to 32 placebo-treated control transplant recipients. In the same study, ALA also improved short-term outcomes of kidney transplantation in a recent retrospective clinical study in which 47 patients were treated with ALA (600 mg) immediately before kidney transplantation who also received 600 mg ALA-perfused renal allograft 1 h prior to transplantation (Osella et al., 2023). Although these clinical studies did not report the mechanisms underlying the renal graft protection by ALA, it is not wrong to suggest that the protective mechanisms by ALA against renal IRI as discussed in section 3.2 above, account for the observed renal graft protection and the improved outcomes of kidney transplantation since IRI is a major contributor to the development of post-transplant complications including renal graft rejection.

3.7. ALA for autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited life-threatening multisystemic and progressive disorder characterized by multiple and bilateral cystic dilation of renal tubules due to mutations in polycystin 1 (PKD1) or polycystin 2 (PKD2) genes (Boerrigter et al., 2021). ADPKD is one of the most prevalent hereditary human illnesses and the most frequent genetic cause of kidney failure in adults. Approximately, 4 to 7 million people have ADPKD worldwide, which accounts for 7–15% of patients receiving renal replacement therapy (Akoh, 2015; Goksu et al., 2023). Early-stage changes such as hypertension, endothelial dysfunction, systemic inflammation, and accelerated atherosclerosis are responsible for increased cardiovascular risks and hasten the onset of ESRD (Lai et al., 2020).

There is a dearth of studies in the literature on the effect of H2S on ADPKD. The only available study is the one by Lai et al. (2020), who recently reported a controlled longitudinal, prospective interventional study involving 33 ADPKD patients who received daily administration of 1.6 g of ALA for 6 months and 26 ADPKD patients with no ALA administration as control group. They observed significant reduction in serum levels of C-reactive protein and pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), uric acid as well as plasma NOX2 and renal resistive index (a renal and systemic vascular damage marker), which partly contributed to improvement in vascular endothelial dysfunction, renal function, and cardiovascular risk factors in ALA-treated ADPKD patients compared to ADPKD control subjects (Lai et al., 2020) (Fig. 1). Recent pre-clinical evidence including those from our research group demonstrate that administration of ALA results in H_2S release from sulfane sulphur (precursor of H_2S) in the homogenates of rat kidneys and other tissues, and increases expression of H_2S-producing enzymes (CBS, CSE and 3-MST), leading to increased renal and plasma H_2S levels under pathological conditions (Bilska et al., 2008; Bilska-Wilkosz et al., 2017; Dugbartey et al., 2022b, 2022d, 2022e). This suggests that ALA can be considered an H_2S-storage compound that releases H_2S in response to biological signals. Although endogenous H_2S level was not measured following administration of ALA in ADPKD patients in the above clinical study, it is possible that the beneficial effect of ALA in this group of patients could be due to increased expression of H_2S-producing enzymes and endogenous H_2S production by ALA along with the potent antioxidant, anti-inflammatory and other therapeutic properties of H_2S.

Burgeoning evidence also suggest that metabolic dysregulations in ADPKD involve abnormal mitochondrial morphology and function and facilitates cyst formation, as seen in increased vacuolated and fragmented mitochondria in $PKD1^{-/-}$ mutant renal epithelial cell lines, mouse and human kidneys and decreased viability and exercise endurance along with increased carbon dioxide production (Ishimoto et al., 2017; Lin et al., 2018). Against this background, the mitochondrial synthesis of ALA and improvement in renal function following its administration in ADPKD patients suggests that ALA may have attenuated pathological events that lead to abnormal renal mitochondrial morphology and function and inhibited cyst formation. Besides, ALA has been reported to increase mitochondrial membrane potential (an indication of improved mitochondrial bioenergetics) and inhibited ROS generation in the mitochondria under pathological conditions (Wang et al., 2013). Furthermore, the H_2S-producing enzyme, 3-MST, is a mitochondrial enzyme, which accounts principally for renal mitochondrial H_2S production, while CBS and CSE (cytosolic H_2S-producing enzymes) translocate to the mitochondria to increase endogenous H_2S

production in response to specific stressful stimuli. Therefore, the observed improvement in renal function in ALA-treated ADPKD patients may imply that ALA may have facilitated CBS and CSE translocation to the mitochondria to increase renal mitochondrial H_2S production via mechanisms that are activated under stressful conditions such as ADPKD (Fig. 1). While this assumption sounds logical and convincing, further studies are needed to validate it.

3.8. ALA for obstructive uropathy

Obstructive uropathy refers to an anatomical or functional blockade along the urinary tract resulting in a disturbance in normal urine flow. The obstruction to normal urine flow causes physiologic and metabolic derangements which affect kidney function. Tseng and Stoller (2009) found that a partial obstruction results in upregulation of angiotensin and AT_1 receptor, leading to increased ureteral peristalsis in an attempt to relieve the obstruction. This may lead to increased distention and intraluminal pressure when the obstruction becomes complete (Tseng and Stoller, 2009). Furthermore, unilateral ureteral obstruction (UUO) has been found to increase interstitial inflammation mediated by macrophages, which attract several cytokines and chemokines as an early response to the obstruction (Misseri et al., 2004; Kluth et al., 2004).

Interestingly, ALA has been found to be useful in treatment of obstructive uropathy. In a rat model of UUO, pre-treatment of UUO rats with ALA significantly reduced ipsilateral hydronephrosis along with improved renal function (markedly reduced serum creatinine and BUN) compared to the sham group without ALA treatment (Wongmekiat et al., 2013). This renal protection corresponded to reduced leukocyte infiltration, renal TGF-β1 expression, and improved renal antioxidant status, which was evidenced by substantial reduction in MDA level and increased levels of GSH and total antioxidant capacity (Wongmekiat et al., 2013). This observation was later confirmed by Cho et al. (2017) in a mouse model of UUO in which ALA treatment markedly attenuated renal fibrosis and UUO-induced epithelial mesenchymal transition (EMT) by decreasing renal expression of TGF-β1, ICAM-1 and NF-κB proteins compared with the sham group. It is important to note that EMT induces renal fibrosis in UUO and destroys tubular basement membrane integrity through upregulation of matrix proteinases such as MMP-2 and MMP-9 (Fig. 1). Remarkably, this pathological change was ameliorated by ALA treatment, characterized by reduction in the expression of these proteinases (Cho et al., 2017). Although further investigations are required to provide a comprehensive understanding of the effects of ALA in the clinical management of obstructive uropathy, these preclinical studies suggest that ALA may have significant potential benefits in attenuating renal injury in obstructive uropathy by reducing metabolic and structural changes that negatively impact kidney function.

4. Toxicity of ALA

ALA is generally regarded as a safe supplement in the management of various immune-mediated conditions. However, as with any other medication or supplement, the main issue regarding the use of ALA is the incidence of overdose. According to a study by Fogacci et al. (2020), adults can safely consume up to 2400 mg of ALA without experiencing any harmful effects. However, although ALA has many potential therapeutic effects, there have been reports of ALA toxicity when ingested at higher than recommended doses (Cremer et al., 2006). Therefore, it is important to note that taking high doses of ALA is not recommended, as it does not provide any additional benefits. A case report by Halabi et al. (2023) described the clinical course of a 42-year-old woman who arrived at the emergency department after intentionally ingesting an overdose of 10 tablets of ALA 600 mg each, resulting in a total intake of 6 g (92.3 mg/kg). The patient exhibited various severe complications, including refractory seizures, metabolic acidosis, thrombocytopenia, rhabdomyolysis, impaired cardiac function, kidney injury, and supraventricular tachycardia (Halabi et al., 2023). Despite receiving multiple interventions such as dual pressors, anti-epileptic medications, high-dose insulin with euglycemia protocol, and methylene blue (at a dose of 1 mg/kg), her condition worsened, ultimately leading to multi-organ failure. Unfortunately, despite aggressive resuscitation efforts, the patient unfortunately did not survive. This case report indicates that just like other pharmacological agents, doses of ALA higher than therapeutic dose can cause organ damage and death.

A new body of evidence points to the fact that ALA has the potential of precipitating neural epidermal growth factor-like 1(NELL)-associated membranous nephropathy. In a recent case report by Nassar et al. (2023), about a type-2 diabetic patient with CKD on ALA supplementation for the management of her neuropathy, she developed high-grade proteinuria (4175 mg/24 h) and with elevated serum creatinine level. Results from her kidney biopsy revealed characteristic features of NELL-1-asssociated membranous nephropathy. Upon discontinuation of ALA for 5 months, her serum creatinine and urine albumin levels markedly improved.

5. Conclusion and future perspectives

A substantial body of preclinical and clinical evidence shows that ALA is beneficial in the treatment of a variety of kidney diseases. However, due to relatively low bioavailability and increased renal clearance, the use of ALA is limited. To address this shortfall, structural analogs of ALA can be synthesized and evaluated to develop relatively longer-lasting and more potent molecules from the parent ALA molecule. A suitable candidate (ALA analog) will go a long way in enhancing the utilization of ALA as a preferred molecule for research into oxidative stress-mediated and metabolic disorders. The next step in this journey is to initiate a global bench-to-bedside translational approach in the relevant clinical settings. Furthermore, the use of ALA in other renal conditions such as nephrotic syndrome, renal cancers and glomerulopathies should be considered.

CRediT authorship contribution statement

George J. Dugbartey: Conceptualization, Writing, Supervision, Figure preparation, Editing and Review. **Karl K. Alornyo:** Writing. **Christabel O. Dapaa-Addo:** Writing. **Emmanuel Botchway:** Writing. **Emmanuel K. Kwashie:** Writing. **Yvonne Harley:** Writing. All authors have read the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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