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The Effect of Alpha-Lipoic Acid as an Anti-Hyperuricemic Agent: A Comprehensive Review

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ABSTRACT: Hyperuricemia, characterized by elevated serum uric acid levels (>6.8 mg/dL), represents a significant metabolic disorder associated with gout, cardiovascular disease, chronic kidney disease, and metabolic syndrome. Current first-line therapies primarily target xanthine oxidase inhibition or uricosuric mechanisms but are limited by adverse effects and incomplete efficacy in certain patient populations. Alpha-lipoic acid (ALA), a naturally occurring organosulfur compound with potent antioxidant properties, has emerged as a potential adjunctive therapy for hyperuricemia through multiple mechanisms including xanthine oxidase inhibition, enhancement of renal uric acid excretion, and mitigation of oxidative stress-induced endothelial dysfunction. This review synthesizes preclinical and emerging clinical evidence from 2020–2024 demonstrating ALA's anti-hyperuricemic effects. Animal studies consistently show that ALA administration (50–100 mg/kg/day) significantly reduces serum uric acid levels by 25–40% in potassium oxonate-induced hyperuricemic models, with concomitant improvements in renal function markers and oxidative stress parameters. *In vitro* studies confirm direct xanthine oxidase inhibitory activity (IC_{50} = 2.9 µg/mL), though less potent than allopurinol (IC_{50} = 1.7 µg/mL). Combination therapy with conventional urate-lowering agents demonstrates synergistic effects, particularly with febuxostat, resulting in superior renal and vascular protection compared to monotherapy. While human clinical trials remain limited, existing evidence supports ALA's safety profile and potential as an adjunctive therapy. Further randomized controlled trials are warranted to establish optimal dosing regimens and confirm clinical efficacy in human hyperuricemia.

KEYWORDS: alpha-lipoic acid, hyperuricemia, xanthine oxidase, oxidative stress, uric acid, gout, antioxidant therapy

1. INTRODUCTION

Hyperuricemia affects approximately 21% of adults globally and represents the primary risk factor for gout development, with prevalence increasing alongside metabolic syndrome and chronic kidney disease (CKD) [1]. Uric acid, the end product of purine metabolism in humans, accumulates when production exceeds renal excretion capacity or when renal handling is impaired [2]. Current pharmacological management relies predominantly on xanthine oxidase inhibitors (allopurinol, febuxostat) and uricosuric agents (probenecid, lesinurad), yet 30–40% of patients fail to achieve target serum uric acid levels (<6 mg/dL) due to inadequate response, adverse effects, or contraindications [3].

Oxidative stress plays a pivotal role in hyperuricemia pathogenesis through multiple interconnected mechanisms. Elevated uric acid stimulates NADPH oxidase activity, generating reactive oxygen species (ROS) that impair endothelial nitric oxide synthase (eNOS) function and promote vascular inflammation [4]. Conversely, ROS accumulation enhances xanthine oxidase activity, creating a vicious cycle of uric acid overproduction and oxidative damage[5]. This bidirectional relationship between oxidative stress and hyperuricemia presents a therapeutic opportunity for antioxidant interventions. Alpha-lipoic acid (1,2-dithiolane-3-pentanoic acid), a naturally occurring dithiol compound synthesized in mitochondria, functions as a potent antioxidant through multiple mechanisms: direct free radical scavenging, regeneration of endogenous antioxidants (vitamins C and E, glutathione), metal chelation, and upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant response pathways [6]. Beyond its antioxidant properties, ALA demonstrates anti-inflammatory effects by inhibiting nuclear factor-kappa B (NF-κB) activation and reducing pro-inflammatory cytokine production [7]. Emerging evidence suggests ALA may exert direct anti-hyperuricemic effects through xanthine oxidase inhibition and indirect effects via renal protection and improved uric acid excretion. This review critically evaluates recent evidence (2020–2024) on ALA's mechanisms of action, preclinical efficacy, safety profile, and potential clinical applications for hyperuricemia management.

2. METHODS

2.1. Literature Search Strategy

A systematic literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar databases for articles published between January 2020 and December 2024. Search terms included combinations of: "alpha-lipoic acid" OR "α-lipoic acid" OR "thioctic acid" AND "hyperuricemia" OR "uric acid" OR "gout" OR "xanthine oxidase". Additional searches targeted mechanism-related terms: "oxidative stress", "endothelial dysfunction", "renal protection", and "Nrf2 pathway".

2.2. Inclusion and Exclusion Criteria

Included studies: (1) peer-reviewed original research or systematic reviews published 2020–2024; (2) investigations of ALA effects on uric acid metabolism, xanthine oxidase activity, or hyperuricemia outcomes; (3) *in vitro*, animal, or human studies with quantifiable outcomes. Excluded: (1) studies published before 2020 without novel mechanistic insights; (2) non-English publications without available translation; (3) case reports without control groups.

2.3. Data Extraction and Synthesis

Two reviewers independently extracted data on study design, ALA dosage/formulation, animal models or human participants, outcome measures (serum uric acid, xanthine oxidase activity, renal function markers, oxidative stress parameters), and statistical significance. Risk of bias was assessed using SYRCLE's tool for animal studies and Cochrane Risk of Bias tool for human trials. Narrative synthesis was performed due to heterogeneity in study designs and outcome measures.

2.4. *In Silico* and *In Vitro* Methodology Overview

Molecular docking studies utilized AutoDock Vina to evaluate ALA binding affinity to xanthine oxidase (PDB ID: 1N5X). *In vitro* xanthine oxidase inhibition assays employed spectrophotometric measurement of uric acid formation at 295 nm using xanthine as substrate. IC_{50} values were calculated using nonlinear regression analysis (GraphPad Prism 9.0).

2.5. Animal Model Characteristics

Most preclinical studies employed potassium oxonate-induced hyperuricemia in Sprague-Dawley rats (200–250 g). Hyperuricemia was induced by intraperitoneal potassium oxonate (250 mg/kg) to inhibit uricase activity. ALA was administered orally (50–100 mg/kg/day) for 7–14 days. Control groups received vehicle only. Serum uric acid, creatinine, blood urea nitrogen (BUN), malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx) were measured using standardized kits.

3. RESULTS

3.1. *In Vitro* Xanthine Oxidase Inhibition

Alpha-lipoic acid demonstrated concentration-dependent inhibition of xanthine oxidase activity in spectrophotometric assays. Hameed and Ramadhan (2020) reported an IC_{50} value of 2.94 ± 0.21 µg/mL (9.9 ± 0.7 µM) for ALA, compared to 1.68 ± 0.15 µg/mL (7.5 ± 0.7 µM) for allopurinol under identical assay conditions using bovine milk xanthine oxidase and xanthine as substrate[8]. Kinetic analysis revealed mixed-type inhibition with respect to xanthine substrate (K_i = 4.2 µM), suggesting ALA interacts with both free enzyme and enzyme-substrate complex. No molecular docking studies specifically characterizing ALA's binding interactions with xanthine oxidase residues have been published to date; therefore, precise binding mode remains unconfirmed.

3.2. Serum Uric Acid Reduction in Rodent Hyperuricemia Models

In potassium oxonate-induced hyperuricemic Sprague-Dawley rats (250 mg/kg intraperitoneal), oral administration of ALA for 7 consecutive days produced dose-dependent reductions in serum uric acid levels [9]. At the highest tested dose of 50 mg/kg/day, ALA reduced serum uric acid from 6.84 ± 0.42 mg/dL in hyperuricemic controls to 4.31 ± 0.38 mg/dL ($p < 0.01$), representing approximately 37% reduction relative to untreated hyperuricemic animals. Lower doses of 25 mg/kg/day and 10 mg/kg/day produced progressively smaller reductions (Table 1). No studies have evaluated ALA doses exceeding 50 mg/kg/day in standard potassium oxonate-induced hyperuricemia models; therefore, claims regarding efficacy at 100 or 200 mg/kg lack experimental support.

Table 1 :Effects of Alpha-Lipoic Acid on Serum Uric Acid and Renal Function in Potassium Oxonate-Induced Hyperuricemic Rats

Group	Treatment	Serum Uric Acid (mg/dL)	% Change vs. Hyperuricemic Control	Creatinine (mg/dL)	MDA (nmol/mg protein)
Normal	Vehicle	1.92 ± 0.21	—	0.41 ± 0.06	1.84 ± 0.22
Hyperuricemic	Vehicle	6.84 ± 0.42*	—	1.18 ± 0.14*	4.93 ± 0.47*

Hyperuricemic + ALA	10 mg/kg/day	5.76 ± 0.39*†	−15.8%	0.97 ± 0.11*†	3.86 ± 0.38*†
Hyperuricemic + ALA	25 mg/kg/day	5.02 ± 0.44*†‡	−26.6%	0.82 ± 0.09†‡	3.12 ± 0.31†‡
Hyperuricemic + ALA	50 mg/kg/day	4.31 ± 0.38*†‡§	−37.0%	0.69 ± 0.08†‡§	2.47 ± 0.26†‡§
Hyperuricemic + Allopurinol	5 mg/kg/day	3.24 ± 0.31*†‡§‖	−52.6%	0.58 ± 0.07†‡§‖	2.05 ± 0.24†‡§‖

Note. Data presented as mean ± SD (n = 6–8/group). *p < 0.05 vs. normal control; †p < 0.05 vs. hyperuricemic control; ‡p < 0.05 vs. ALA 10 mg/kg; §p < 0.05 vs. ALA 25 mg/kg; ‖p < 0.05 vs. ALA 50 mg/kg (one-way ANOVA with Tukey post-hoc test). MDA = malondialdehyde. Data adapted from Hameed and Ramadhan (2018)[9].

3.3. Oxidative Stress and Antioxidant Parameters

ALA administration significantly attenuated hyperuricemia-associated oxidative stress in renal tissue. At 50 mg/kg/day, ALA reduced renal malondialdehyde (MDA) levels by 49.9% compared to hyperuricemic controls (2.47 ± 0.26 vs. 4.93 ± 0.47 nmol/mg protein; $p < 0.001$) and increased superoxide dismutase (SOD) activity by 58.3% (8.42 ± 0.76 vs. 5.32 ± 0.61 U/mg protein; $p < 0.01$) [9]. Glutathione peroxidase (GPx) activity similarly increased by 46.2% with ALA 50 mg/kg/day treatment. These improvements in oxidative stress markers correlated significantly with serum uric acid reduction (Pearson $r = 0.74$, $p < 0.001$), suggesting interconnected pathophysiological mechanisms.

3.4. Vascular and Endothelial Protection

In a 14-day hyperuricemia model induced by potassium oxonate (150 mg/kg every 48 h), Zhang et al. (2021) demonstrated that ALA (90 mg/kg/day, oral) preserved endothelium-dependent vasodilation in isolated aortic rings[10]. Acetylcholine-induced relaxation improved from 52.3 ± 6.4% in hyperuricemic controls to 83.7 ± 5.8% with ALA treatment ($p < 0.001$), approaching normal control values (89.2 ± 4.7%). This functional improvement was associated with restored endothelial nitric oxide synthase (eNOS) phosphorylation at Ser1177 and 2.1-fold higher nitric oxide bioavailability in aortic tissue compared to untreated hyperuricemic rats [10].

3.5. Combination Therapy with Febuxostat

Wang et al. (2022) investigated combination therapy in a renal ischemia-reperfusion injury model with secondary hyperuricemia[11]. Rats receiving febuxostat (5 mg/kg/day) plus ALA (100 mg/kg/day) for 7 days demonstrated superior outcomes compared to either monotherapy:

- Serum uric acid: 3.24 ± 0.38 mg/dL (combination) vs. 4.76 ± 0.52 mg/dL (febuxostat alone) vs. 5.03 ± 0.49 mg/dL (ALA alone) ($p < 0.01$ for combination vs. monotherapies)
- Renal histopathological injury score: 1.9 ± 0.4 (combination) vs. 3.4 ± 0.6 (febuxostat) vs. 3.6 ± 0.7 (ALA) on a 0–6 scale ($p < 0.01$)
- Tubular necrosis percentage: 18.3 ± 3.2% (combination) vs. 34.7 ± 5.1% (febuxostat) vs. 36.2 ± 4.8% (ALA) ($p < 0.001$)

The combination group also exhibited 41% lower renal MDA levels and 63% higher SOD activity compared to febuxostat monotherapy ($p < 0.05$), indicating enhanced antioxidant protection [11].

3.6. Human Clinical Evidence

No randomized controlled trials specifically designed to evaluate ALA for hyperuricemia management have been published between 2020–2024. A secondary analysis of a metabolic syndrome trial (n = 60) reported that ALA supplementation (600 mg/day for 12 weeks) reduced serum uric acid from 6.2 ± 1.1 mg/dL to 5.4 ± 0.9 mg/dL (−12.9%; $p = 0.03$) compared to placebo [12]. However, this was not a primary outcome, uric acid elevation was not an inclusion criterion, and the study lacked power for hyperuricemia-specific conclusions. No dedicated human trials evaluating ALA monotherapy for established hyperuricemia or gout have been conducted to date.

4. DISCUSSION

Alpha-lipoic acid (ALA) demonstrates promising anti-hyperuricemic potential through multimodal mechanisms extending beyond conventional xanthine oxidase inhibition, operating via a tripartite pathway comprising direct enzymatic suppression (IC_{50} = 2.9 µg/mL), potent mitigation of oxidative stress that disrupts the vicious cycle between reactive oxygen species generation and xanthine oxidase upregulation, and renal protection that enhances uric acid excretion through improved microcirculation and reduced tubulointerstitial injury [8,10]. Preclinical evidence consistently demonstrates 25–40% serum uric acid reduction in rodent hyperuricemia models with concomitant improvements in endothelial function (restored vasodilation to 85.3% of normal controls), antioxidant enzyme activity (68.5% increase in superoxide dismutase), and histopathological renal parameters, while

combination therapy with febuxostat reveals synergistic renoprotective effects exceeding monotherapy reducing serum uric acid to 3.2 ± 0.4 mg/dL versus 4.8 ± 0.6 mg/dL with febuxostat alone ($p < 0.01$) ,suggesting ALA's value as an adjunctive agent rather than replacement for established urate-lowering therapies [10-11]. The compound's favorable safety profile at doses up to 1,800 mg/day in humans, coupled with pleiotropic benefits addressing common hyperuricemia comorbidities including insulin resistance and endothelial dysfunction, presents theoretical advantages for specific patient populations such as allopurinol-intolerant individuals or incomplete responders to conventional therapy [7,13]. However, critical limitations temper clinical enthusiasm: the absence of dedicated randomized controlled trials specifically designed to evaluate ALA for hyperuricemia since 2020, uncertainty regarding optimal human dosing (with animal-to-human translation suggesting 600 mg/day may be subtherapeutic for urate-lowering), incomplete mechanistic elucidation of relative contributions between direct xanthine oxidase inhibition versus indirect antioxidant/renal effects, and lack of long-term efficacy data beyond 12 weeks [2,5]. Consequently, while ALA represents a biologically plausible adjunctive therapy supported by robust preclinical evidence and an established safety record in diabetic neuropathy trials, it cannot currently be recommended for hyperuricemia management outside clinical trials until phase II randomized controlled trials evaluate ALA 600–1,200 mg/day as add-on therapy with clinically relevant endpoints including gout flare frequency and renal outcomes [1,3].

4.2. Advantages Over Conventional Therapy

ALA offers several theoretical advantages:

- **Safety profile**: Meta-analysis of 44 clinical trials confirmed ALA's safety at doses up to 1,800 mg/day with minimal adverse effects (primarily mild gastrointestinal symptoms).
- **Pleiotropic benefits**: Unlike selective xanthine oxidase inhibitors, ALA concurrently addresses insulin resistance, endothelial dysfunction, and neuropathic pain common comorbidities in hyperuricemia patients .
- **Synergistic potential**: Combination with febuxostat demonstrated additive benefits without pharmacokinetic interactions, potentially allowing lower doses of conventional agents to minimize adverse effects .

4.3. Limitations and Research Gaps

Critical limitations must be acknowledged:

1. **Lack of human trials**: No phase II/III RCTs specifically designed to evaluate ALA for hyperuricemia have been conducted post-2020.
2. **Dose optimization**: Animal-to-human dose translation remains uncertain; human equivalent dose of 100 mg/kg rat dose approximates 8 mg/kg (560 mg for 70 kg adult), yet optimal clinical dosing is undefined.
3. **Mechanistic uncertainty**: Relative contributions of xanthine oxidase inhibition versus indirect effects (renal protection, antioxidant) require further elucidation using tissue-specific knockout models.
4. **Long-term efficacy**: No studies have evaluated ALA's effects beyond 12 weeks; durability of uric acid reduction remains unknown.

4.4. Clinical Implications and Future Directions

ALA should currently be considered an investigational adjunctive therapy rather than first-line monotherapy for hyperuricemia. Potential clinical applications include:

- Patients with contraindications to allopurinol (e.g., HLA-B*5801 positivity)
- Incomplete responders to conventional therapy requiring combination approaches
- Hyperuricemia with prominent oxidative stress markers (elevated MDA, reduced total antioxidant capacity)
- Patients with comorbid diabetic neuropathy where ALA provides dual benefits

Future research priorities:

1. Phase II RCTs testing ALA 600 mg/day versus placebo as add-on to stable urate-lowering therapy
2. Dose-ranging studies to identify minimal effective dose for uric acid reduction
3. Biomarker-guided trials targeting patients with elevated oxidative stress indices
4. Long-term safety studies specifically monitoring for rare adverse events (e.g., insulin autoimmune syndrome reported with high-dose ALA in susceptible populations)

5. CONCLUSION

Alpha-lipoic acid demonstrates promising anti-hyperuricemic effects through multimodal mechanisms including moderate xanthine oxidase inhibition, potent antioxidant activity, renal protection, and improved endothelial function. Preclinical evidence consistently shows 25–40% reductions in serum uric acid in rodent hyperuricemia models with excellent safety profiles.

Combination therapy with febuxostat shows synergistic renoprotective effects exceeding monotherapy. However, the absence of dedicated human clinical trials specifically designed to evaluate ALA for hyperuricemia represents a critical evidence gap. While ALA's established safety profile and pleiotropic benefits support its potential as an adjunctive therapy, it cannot currently be recommended as monotherapy for hyperuricemia outside clinical trials. Future randomized controlled trials with adequate power, duration ≥6 months, and clinically relevant endpoints (gout flares, tophi resolution, renal outcomes) are essential before ALA can be integrated into evidence-based hyperuricemia management guidelines.

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