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Review

Alpha-Lipoic Acid in Experimental Colitis: Redox Regulation, Ferroptosis, Epithelial Barrier Function, and Gut Microbiota

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Abstract

Preclinical studies suggest that α-lipoic acid (ALA) can reduce oxidative and inflammatory injury, support epithelial barrier function, and alter gut microbiota in experimental colitis, although evidence for ferroptosis as a required mediator remains limited. This narrative review distinguishes free ALA from andrographolide–lipoic acid conjugates and lipoic acid-containing materials, evaluates the limits of mechanistic inference, and emphasizes that clinical efficacy in ulcerative colitis has not been established by publicly available trial results.

Keywords: alpha-lipoic acid; experimental colitis; ulcerative colitis; redox signaling; ferroptosis; epithelial barrier; gut microbiota

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colonic mucosa in which genetic susceptibility, environmental exposure, epithelial dysfunction, immune activation, and altered host–microbiota interactions converge on recurrent mucosal injury [1,2]. The global expansion of inflammatory bowel disease (IBD) into newly industrialized regions has transformed UC from a predominantly Western disorder into a worldwide health challenge [3]. Treatment goals have correspondingly moved beyond symptom control toward sustained steroid-free remission, biomarker normalization, and endoscopic healing within a treat-to-target framework [4]. These goals remain incompletely achieved, and substantial disease burden, recurrent flares, and diagnostic delay persist despite therapeutic progress [5].

Available UC therapies include 5-aminosalicylates, corticosteroids, immunomodulators, biologics, Janus kinase inhibitors, and sphingosine-1-phosphate receptor modulators [6,7]. Despite these options, incomplete response and persistent mucosal inflammation remain reasons to investigate complementary approaches [8–10].

Here, the clinical context is UC, but the evidence assessed is predominantly from experimental colitis and epithelial cell systems. These models reproduce selected features of intestinal injury and should not be described as equivalent to human UC.

α-Lipoic acid (ALA; thioctic acid) is an endogenous disulfide-containing compound whose protein-bound form serves as a mitochondrial enzyme cofactor. Administered free ALA and its reduced form, dihydrolipoic acid (DHLA), influence cellular redox reactions and stress responses [11,12]. These properties provide a rationale for examining ALA in epithelial oxidative injury, barrier dysfunction, and intestinal inflammation.

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This review evaluates how well the experimental findings support the proposed mechanisms of ALA in colitis. Its contribution is to distinguish evidence for free ALA from evidence for chemically distinct derivatives and materials, and to separate observed biological responses from mechanisms shown to be required for protection. Recent ferroptosis and microbiota-transfer studies are considered alongside epithelial repair experiments. Table 1 summarizes free-ALA studies; Figures 1 and 2 distinguish host responses from microbiota-related findings; and Table 2 compares intervention classes.

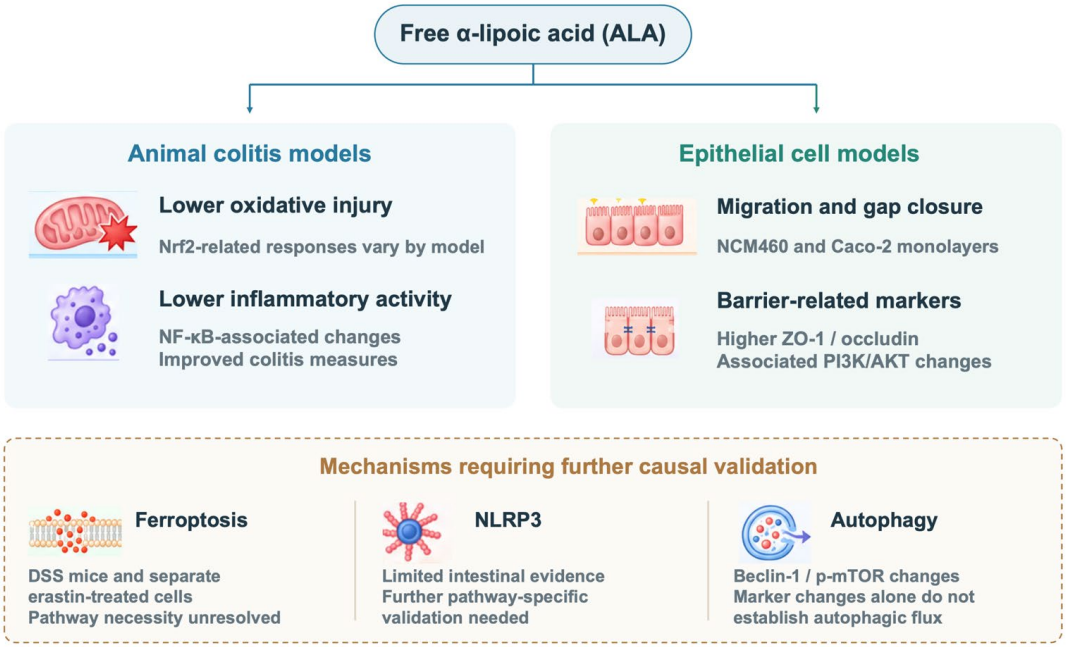


Figure 1. Host responses associated with free ALA in experimental systems. The diagram separates observations in colitis models from epithelial cell findings and highlights the limited evidence for ferroptosis, NLRP3, and autophagy-related mechanisms. Solid arrows connect ALA exposure with reported responses; they do not indicate direct binding or establish pathway necessity. The dashed panel identifies mechanisms requiring further causal validation. Abbreviations: ALA, α-lipoic acid; DSS, dextran sulfate sodium; Nrf2, nuclear factor erythroid 2-related factor 2; NF-κB, nuclear factor kappa B; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; ZO-1, zonula occludens-1; NLRP3, NLR family pyrin domain containing 3; p-mTOR, phosphorylated mechanistic target of rapamycin.

Literature Search and Selection

This narrative review uses a focused, non-systematic selection of studies relevant to ALA and intestinal injury. During revision, targeted searches of PubMed-indexed records and publisher websites were updated on 24 October 2026 using combinations of alpha-lipoic acid, lipoic acid, thioctic acid, colitis, ulcerative colitis, ferroptosis, epithelial barrier, and microbiota. The existing bibliography provided additional starting points. Primary colitis studies and epithelial experiments were prioritized for intervention-specific claims; reviews provided background, and material-based studies were assessed separately. The full reports by Trivedi and Jena, Sun and Sun, Jiang et al., Taner et al. and Huang et al. [13–17] were checked for induction protocols, ALA exposure, outcome measurements, and experimental comparisons. ClinicalTrials.gov was checked for NCT06067698. No new meta-analysis, formal risk-of-bias assessment, or exhaustive systematic search was undertaken. Details that were not reported or were inconsistent within a source were identified rather than inferred. ChatGPT assisted with English editing, paragraph organization, matching in-text citation numbers to reference entries, and refining the layout and label placement of figures. The authors independently assessed whether each cited source was relevant and supported

the corresponding statement. The authors reviewed the output and checked scientific statements against the cited sources.

2. Redox Pharmacology and Scope of the Evidence

2.1. Pharmacology of Free ALA

Endogenous lipoic acid functions as a covalently bound cofactor within mitochondrial dehydrogenase complexes. Exogenous ALA is instead administered as a small redox-active molecule that is rapidly absorbed, extensively metabolized, and reduced intracellularly to DHLA [11,12]. Food intake, stereochemistry, formulation, and first-pass metabolism influence exposure. For UC, these features matter because systemic pharmacology does not imply sustained luminal or mucosal exposure in the colon.

ALA affects several redox-sensitive processes, but the direction of a pathway response can depend on the cell type and injury model. Changes in reactive oxygen species (ROS), reactive nitrogen species (RNS), or downstream proteins should therefore be interpreted within the experimental conditions rather than as evidence of a universal molecular target.

2.2. Distinct Compounds and Experimental Systems

The most disease-proximal evidence comes from studies in which free ALA was administered in experimental colitis. Across dextran sulfate sodium (DSS), 2,4,6-trinitrobenzenesulfonic acid (TNBS), and acetic-acid models, ALA administration was associated with less histological injury and changes in redox, inflammatory, or barrier-associated measures [13–17]. Table 1 summarizes these studies together with the epithelial models most informative for mechanism while preserving the distinction between direct colitis evidence and supportive in vitro evidence.

The systematic review by Moeinian et al. included both free ALA and andrographolide–lipoic acid-1 (AL-1), a chemically distinct conjugate [18]. Improvements were reported for some outcomes, but the pooled estimates for tumor necrosis factor-α (TNF-α; $p = 0.13$) and myeloperoxidase activity ($p = 0.77$) were not statistically significant. Differences in compounds, species, induction protocols, doses, and treatment schedules limit a single interpretation of the findings. This review therefore does not treat that meta-analysis as a pooled efficacy estimate for free ALA alone.

A second evidence domain comprises intestinal epithelial models that resolve repair biology without reproducing the immune and microbial complexity of colitis. In NCM460 and Caco-2 cells, ALA accelerated wound closure and increased zonula occludens-1 (ZO-1) and occludin, whereas a heat-stress Caco-2 model showed preservation of transepithelial integrity and epithelial repair [19,20]. These experiments strengthen mechanistic plausibility, although they do not constitute independent evidence of therapeutic efficacy in UC.

A third domain includes lipoic-acid-containing polymers, nanoparticles, and adhesive materials. In these systems, lipoic acid can function as a structural monomer, redox-responsive linker, adhesive component, or element of a composite carrier. Efficacy may therefore derive from tissue retention, cargo delivery, material mechanics, or local barrier effects rather than from free-ALA pharmacology. Pooling these platforms with the parent compound would overstate the evidence for ALA itself.

DSS injury depends on concentration, molecular weight, exposure duration, strain, and husbandry, so a single maximum DSS dose is not a meaningful criterion for model validity [21]. Table 1 specifies induction and treatment schedules verified from the full reports. These schedules range from concurrent ALA and DSS exposure to treatment started after chemical induction. Differences in timing and model severity limit direct comparisons, while unreported or internally inconsistent details remain identified in the table notes.

Table 1. Representative studies of free ALA in experimental colitis and intestinal epithelial models.

Study	Model/Exposure	Principal Finding	Interpretive Value
Trivedi and Jena, 2013 [13]	Male Swiss mice, 25–28 g; 3% DSS (36–40 kDa) on days 1–7 and 22–28, with water on days 8–21. Oral ALA: 20, 40, or 80 mg/kg/day on days 1–28 (n = 8/group), or 80 mg/kg for 14 or 28 days after the second DSS cycle.	Less disease activity, histological injury, lipid peroxidation, DNA damage, and collagen staining; higher glutathione, Nrf2/NQO1, and occludin; lower inflammatory markers and plasma lipopolysaccharide.	Concurrent and post-induction protocols. Broad marker associations; permeability and pathway necessity were not directly tested.
Sun and Sun, 2016 [14]	Male BALB/c mice, 22–25 g; n = 10/group. Intrarectal TNBS, 3 mg in 0.12 mL ethanol. ALA 80 mg/kg/day by oral gavage for 7 days, starting 24 h after induction.	Improved disease activity and histology; increased Beclin-1 and reduced phosphorylated mTOR.	Autophagy-related protein changes; these measures do not establish autophagic flux or pathway necessity.
Jiang et al., 2024 [15]	Female C57BL/6 mice (6–8 weeks; n = 6/group); 3% DSS (36–50 kDa) in drinking water for 7 days. ALA 25, 50, or 100 mg/kg by oral gavage daily on days 1–7; assessed on day 8.	Improved disease measures; lower ferrous iron and lipid-peroxidation products; restored glutathione, GPX4, and xCT; increased nuclear Nrf2 and reduced Keap1.	Concurrent intervention during DSS exposure. Associated markers support reduced ferroptosis-related injury but do not establish necessity.
Jiang et al., 2024 [15], in vitro	Caco-2 cells; 1 μM erastin for 6 h after 30-min pretreatment with 50 μM ALA. Comparators: ferrostatin-1 (0.5 μM) and GSK2606414 (1 μM).	Preserved glutathione, GPX4, and xCT; reduced endoplasmic reticulum stress and apoptosis-related changes.	Pharmacological comparisons support linked responses; causal order and necessity for protection in DSS colitis remain untested.
Taner et al., 2025 [16]	Male Wistar albino rats, 8 weeks, 210–280 g; 34 in total. Intrarectal 4% acetic acid, 2 mL. ALA 100 mg/kg/day, mesalamine 50 mg/kg/day, or both by oral gavage for 14 days, starting 24 h after induction.	ALA-containing regimens improved selected oxidative/nitrosative and histological measures. Combination treatment lowered DRP1 versus untreated colitis; PINK1 reduction was not significant.	Post-induction treatment. Protein abundance does not establish restored mitochondrial dynamics; synergy was not demonstrated.
Huang et al., 2026 [17]	Male C57BL/6J mice, 8 weeks; 2.5% DSS for 7 days, then water for 4 days. ALA 40 or 80 mg/kg in corn oil by oral gavage over days 0–11. Main disease outcomes: n = 7–8; microbial/SCFA analyses and FMT: n = 6.	Improved histological and barrier-associated measures. At 80 mg/kg: altered microbial composition, higher Shannon diversity and cecal SCFAs. FMT recipients showed less severe colitis and higher colonic SCFAs.	Fecal transfer supports a community contribution but does not isolate microorganisms from soluble constituents. FMT timing is internally inconsistent; see note.
Özkan et al., 2025 [22]	Male Wistar rats (8–10 weeks; n = 6 controls, 7/experimental group); 2 mL intrarectal 4% acetic acid. After 24 h, oral gavage of ALA 100 mg/kg/day, mesalamine 50 mg/kg/day, or both for 14 days.	Lower serum and colonic NLRP3 levels and improved colonic SOD measures; combination effects varied by endpoint.	NLRP3 abundance was measured; inflammasome activation and pathway dependence were not directly tested.
Yang et al., 2022 [19]	NCM460 and Caco-2 monolayer gap-closure and migration assays.	Increased migration, wound closure, ZO-1, and occludin; reduced PI3K/AKT, JNK, and p38 signaling in NCM460 cells.	Mechanistic epithelial evidence, not a colitis efficacy model.
Varasteh et al., 2018 [20]	Heat-stressed Caco-2 monolayers	Preserved barrier integrity and epithelial repair; reduced inflammatory responses; context-dependent Nrf2 regulation.	Supportive epithelial evidence showing that beneficial barrier effects need not coincide with uniform Nrf2 activation.

In Huang et al. [17], DSS molecular weight and ALA dosing frequency in the main experiment were not reported. Huang et al. [17] report different timings for DSS exposure relative to FMT in their Methods (Section 2.3) and study diagram (Figure 8A). Wound closure in cell assays refers to reduction in a monolayer gap, not clinical mucosal healing. Abbreviations: DSS, dextran sulfate sodium; TNBS, 2,4,6-trinitrobenzenesulfonic acid; FMT, fecal microbiota transplantation; SCFA, short-chain fatty acid; GPX4, glutathione peroxidase 4; xCT, cystine/glutamate antiporter light chain; SOD, superoxide dismutase; NQO1, NAD(P)H quinone oxidoreductase 1; DRP1, dynamin-related protein 1; PINK1, PTEN-induced kinase 1.

3. Host Responses and Proposed Mechanisms

3.1. Context-Dependent Keap1–Nrf2 Responses

Nuclear factor erythroid 2-related factor 2 (Nrf2) regulates antioxidant and cytoprotective responses relevant to epithelial injury [23]. In the repeated-DSS model of Trivedi and Jena, concurrent and post-induction ALA treatment increased colonic Nrf2 and NAD(P)H quinone oxidoreductase 1 (NQO1) protein levels alongside higher glutathione and lower

lipid-peroxidation measures [13]. Jiang et al. reported increased nuclear Nrf2 and heme oxygenase-1, with reduced Kelch-like ECH-associated protein 1 (Keap1) expression [15]. These observations support an association with Nrf2-related antioxidant responses, but do not establish direct binding of ALA to Keap1 or Nrf2 or show that this pathway is required for protection.

In heat-stressed Caco-2 cells, ALA preserved epithelial integrity while attenuating the stress-induced increase in Nrf2 expression and nuclear translocation [20]. Thus, improved barrier function does not consistently coincide with increased Nrf2 activity. The direction of the Nrf2 response appears to depend on the model and stress conditions.

3.2. Limited Evidence for Ferroptosis as a Mediator

Ferroptosis is an iron-dependent form of regulated cell death driven by phospholipid peroxidation and constrained by glutathione- and glutathione peroxidase 4 (GPX4)-dependent antioxidant systems [24,25]. In UC, it provides a plausible mechanistic link among oxidative stress, altered iron handling, mitochondrial dysfunction, lipid peroxidation, and epithelial injury at the mucosal surface [26]. This connection makes ferroptosis particularly relevant to the redox pharmacology of ALA.

Jiang et al. studied female C57BL/6 mice given 3% DSS for 7 days and ALA at 25, 50, or 100 mg/kg by daily oral gavage on days 1–7 [15]. ALA improved disease measures, reduced colonic ferrous iron and lipid-peroxidation products, and restored glutathione, GPX4, and the cystine transporter xCT. These changes are consistent with less ferroptosis-associated injury. Because ALA was given during DSS exposure, this experiment evaluated concurrent intervention rather than treatment of established colitis.

In the separate cell experiment, Caco-2 cells were pretreated with 50 μM ALA for 30 min before exposure to 1 μM erastin for 6 h [15]. ALA preserved GPX4, xCT, and glutathione and reduced endoplasmic reticulum stress and apoptosis-related changes. Comparisons with ferrostatin-1 (0.5 μM) and the protein kinase R-like endoplasmic reticulum kinase (PERK) inhibitor GSK2606414 (1 μM) provided pharmacological support for a relationship between these responses. However, the experiments did not establish their causal order or show that disrupting Nrf2 or GPX4 removes the protective effect of ALA. Neither the cell comparisons nor the animal marker changes demonstrate that ferroptosis suppression is required for protection in vivo.

3.3. Epithelial Barrier Function and Repair

Barrier failure is not simply a consequence of inflammation. Tight-junction disruption, defective restitution, and impaired mucus-associated defense increase luminal antigen exposure and can perpetuate mucosal immune activation [27–29]. The mucus layer is itself an active component of host defense, and its disruption increases epithelial exposure to microbial products [30]. For an adjunctive candidate such as ALA, recovery of epithelial function is therefore more informative than improvement in systemic antioxidant indices alone.

In NCM460 and Caco-2 cells, ALA increased migration, closure of an experimentally created monolayer gap, and expression of zonula occludens-1 (ZO-1) and occludin [19]. In NCM460 cells, these responses accompanied reduced phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), c-Jun N-terminal kinase (JNK), and p38 signaling [19]. Here, wound closure denotes a measured cell-culture endpoint, whereas epithelial repair includes broader recovery of barrier structure and function. In heat-stressed Caco-2 monolayers, ALA also preserved barrier integrity [20]. Neither cell system establishes mucosal healing in patients.

The in vivo barrier findings require a distinction between structural markers and functional permeability. Trivedi and Jena found greater colonic occludin staining and lower plasma lipopolysaccharide after ALA treatment [13]. Huang et al. reported preservation

of goblet cells, higher Muc2 expression, and increased ZO-1 and occludin staining [17]. Neither study directly measured transepithelial permeability with a tracer-flux assay, so these findings support barrier preservation without demonstrating restored permeability or excluding indirect effects of reduced inflammation. Organoids and epithelial-immune co-cultures, combined with transepithelial resistance, paracellular flux, junctional localization, and cell-death profiling, could help distinguish primary epithelial effects from secondary recovery.

3.4. Inflammatory and Autophagy-Related Responses

Inflammatory cytokines contribute to intestinal injury, although their effects depend on cellular and disease context [31]. In DSS colitis, Trivedi and Jena found lower colonic nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), and signal transducer and activator of transcription 3 (STAT3) protein levels, together with lower interleukin-17 (IL-17), IL-6, and TNF-α [13]. These measurements do not establish reduced transcription-factor activity. Huang et al. more specifically measured a lower phosphorylated-p65/total-p65 ratio, accompanied by reduced COX-2, inducible nitric oxide synthase, and proinflammatory cytokines [17]. Together, these findings support an anti-inflammatory response without identifying a single necessary target.

Evidence for NLR family pyrin domain containing 3 (NLRP3) is narrower. In acetic-acid colitis, ALA, alone or with mesalamine, reduced serum and colonic NLRP3 levels [22]. These protein measurements do not directly establish inflammasome activation or its requirement for protection. In a nonintestinal system, ALA reduced expression of NLRP3 and apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), together with IL-1β release, in activated Kupffer cells [32]. This finding provides supportive evidence, but NLRP3 dependence has not been demonstrated in ALA-treated colitis.

In TNBS colitis, Sun and Sun started oral ALA at 80 mg/kg/day 24 h after induction and continued treatment for 7 days [14]. Improved disease activity and histology accompanied increased Beclin-1 expression and reduced phosphorylated mechanistic target of rapamycin (mTOR). These endpoints indicate altered autophagy-related signaling; they do not measure autophagic flux or establish that autophagy is required for protection. Figure 1 summarizes the main host responses and places the more limited mechanistic evidence separately.

4. Microbiota Contribution and Unresolved Mediators

Fecal microbiota transplantation (FMT) has been studied in randomized trials in patients with UC [33]. Altered microbial composition and interactions with mucosal immunity are recurrent findings in IBD [34,35]. Human mucosal profiling also links host transcriptional patterns and microbial composition with clinical phenotypes [36]. For ALA, changes in community composition need to be related to microbial function and host outcomes before a specific protective mechanism can be assigned.

Huang et al. administered oral ALA at 40 or 80 mg/kg during a protocol comprising 7 days of 2.5% DSS and 4 days of recovery [17]. Microbial profiling and cecal short-chain fatty acid (SCFA) analyses focused on the 80 mg/kg group, which showed higher Shannon diversity and higher acetate, propionate, and butyrate concentrations than the DSS group. In a separate FMT experiment, donors received 80 mg/kg ALA or vehicle for 10 days. Recipients underwent 5 days of antibiotic treatment and a 2-day washout before receiving fecal suspensions for 7 days. Transfer from ALA-treated donors was associated with less severe colitis and higher SCFA concentrations in colonic contents. The relative timing of FMT and recipient DSS exposure is reported inconsistently, as noted in Table 1.

Separately, patient-derived *Enterococcus faecium* strains showed an association between lipoic acid metabolism pathways and inflammatory or probiotic strain groupings; oral free

ALA improved colitis in colonized *Il10*-deficient mice [37]. The strain association does not establish that bacterial lipoic acid metabolism caused the different phenotypes.

These transfer results are consistent with a microbial contribution, but fecal suspensions also contain soluble metabolites and potentially residual administered compound. Without controls that separate these components, FMT does not identify the organism or metabolite responsible for protection. Measured SCFA concentrations also reflect absorption, microbial and host utilization, transit, and excretion; they are not production-rate measurements. Independent experiments show that butyrate can promote regulatory T-cell differentiation [38] and support epithelial barrier function [39], but neither mechanism has been established as necessary for ALA-mediated protection. Clinical FMT studies [40,41] and experimental analyses of microbiota and metabolites [42] support the relevance of microbial function while underscoring the need to identify specific mediators. Figure 2 distinguishes these levels of evidence.

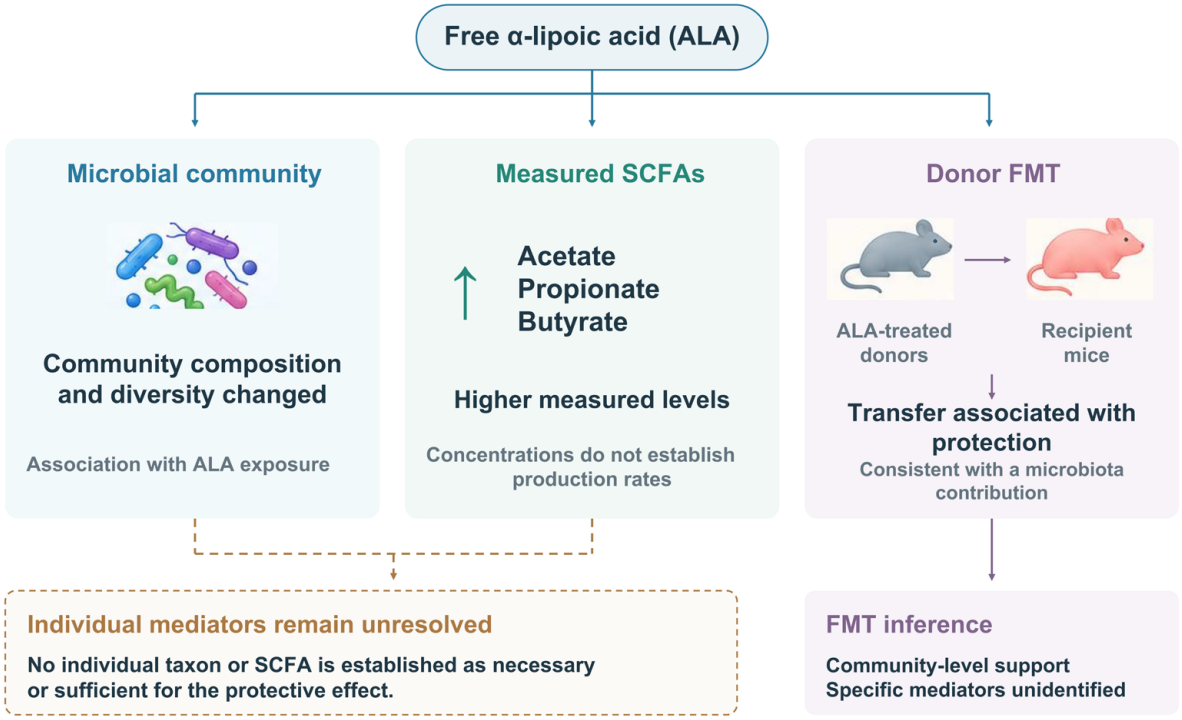


Figure 2. Microbiota-related findings and limits of causal inference for free ALA. In Huang et al. [17], microbial profiling and cecal SCFA analyses focused on mice receiving 80 mg/kg ALA. Fecal transfer from ALA-treated donors was associated with protection and higher SCFA concentrations in recipient colonic contents. Solid arrows indicate observed experimental relationships; dashed connections indicate unresolved contributions of individual taxa or metabolites. Fecal transfer does not isolate viable microorganisms from soluble constituents, and higher SCFA concentrations do not establish increased production rates. Abbreviations: ALA, α-lipoic acid; SCFA, short-chain fatty acid; FMT, fecal microbiota transplantation.

5. Lipoic-Acid-Containing Materials

In delivery systems, the lipoic-acid moiety may serve as a structural component rather than as the administered free compound. Examples include ALA-grafted polysaccharide nanoparticles carrying ginsenoside Rh2 [43] and a chitosan–ALA copolymer/alginate-coated zein carrier for astaxanthin [44]. Both use pH and redox responsiveness. Other platforms use polymerized lipoic acid for local retention and release [45] or as a self-solidifying adhesive barrier [46]. Their effects combine material properties, delivery, and, where present, cargo activity.

Free ALA, AL-1, and lipoic-acid-containing materials are distinct interventions. A benefit observed with a conjugate or carrier cannot be attributed to free ALA without an appropriate comparison. Table 2 makes this distinction explicit.

Colon-targeted delivery may improve local exposure, but comparisons should include free ALA, matched carrier controls, and dose-normalized formulations. Measurements of colonic exposure are needed to determine whether a material improves delivery, changes pharmacological activity, or provides an independent physical barrier.

Table 2. Interpretation of free ALA, AL-1, and lipoic-acid-containing materials.

Intervention Class	Role of Lipoic Acid	What the Experiment Tests	Valid Inference
Free ALA	Parent compound is the active intervention	Dose-, route-, stereochemistry-, and exposure-dependent pharmacology of ALA	Supports mechanistic claims about ALA when disease model and endpoints are appropriate
AL-1 [18]	Andrographolide–lipoic acid conjugate	Pharmacology of a chemically distinct conjugate	Cannot be treated as an interchangeable dose or efficacy estimate for free ALA
ALA-grafted polysaccharide nanoparticles [43]	ALA is part of a pH- and redox-responsive carrier that delivers ginsenoside Rh2	Composite effects of carrier chemistry, targeting, payload, and lipoic-acid moiety	Cannot be interpreted as evidence that free oral ALA reproduces the same efficacy or mechanism
Chitosan-ALA copolymer/alginate-coated zein nanoparticles [44]	The ALA moiety forms part of a pH and redox-responsive carrier; astaxanthin is the bioactive cargo.	Composite effects of carrier architecture, oral delivery, astaxanthin activity, safety, and microbiota modulation	Supports formulation design; cannot be interpreted as evidence for free ALA monotherapy
Self-polymerized lipoic-acid nanodrug [45]	Lipoic acid is polymerized into a colon-retentive therapeutic material that depolymerizes intracellularly	Local retention, redox response, release kinetics, and lipoic-acid pharmacology are coupled	Requires exposure-normalized comparison with free ALA before attributing superiority to mechanism
Poly(lipoic-acid) adhesive [46]	Lipoic acid forms a self-solidifying mucosal barrier	Adhesive, barrier, pathogen-resistant, and redox effects coexist	Represents a distinct material therapeutic entity rather than parent-compound evidence

6. Priorities for Clinical Translation

6.1. Causality and Cell Specificity

Most ALA studies measure bulk tissue markers, which cannot identify the cell population required for protection. Studies of intestinal stem cells and Paneth cells outside colitis suggest that epithelial context influences ALA responses [47,48], but these findings do not establish efficacy in inflamed colon.

Single-cell or spatial analyses [49] could help locate responses within the mucosa. They should be paired with pathway perturbation and functional barrier measurements [50], because a cell-state association alone does not establish a therapeutic mechanism.

6.2. Dose, Exposure, and Formulation

Animal doses cannot be directly converted into an effective patient dose. For scale only, mouse doses of 20–100 mg/kg correspond to approximately 1.6–8.1 mg/kg in an adult using body-surface-area factors of 3 for mice and 37 for humans, or about 97–486 mg

for a 60-kg adult [51]. This calculation is an illustrative human-equivalent dose, not an efficacy prediction or a safe starting-dose recommendation. Route, formulation, metabolism, and colonic exposure can differ substantially between species. The registered UC trial protocol specified 600 mg/day [52], but numerical comparison does not establish equivalent tissue exposure.

Because oral ALA is rapidly absorbed and metabolized [12], plasma and colonic exposure should be measured where feasible. Concurrent dosing should also be distinguished from post-induction treatment. Trivedi and Jena included ALA treatment for 14 or 28 days after the second DSS cycle [13]; Sun and Sun and Taner et al. started treatment 24 h after TNBS or acetic-acid induction, respectively [14,16]. These protocols provide evidence beyond concurrent chemical exposure, but recovery from experimentally induced injury remains different from treatment of established human UC.

6.3. Human Evidence, Combination Therapy, and Safety

Human efficacy remains unestablished by publicly available results. On 24 October 2026, the official record for NCT06067698 listed the randomized, single-blind Tanta University trial as Completed, with 60 participants, actual study completion on 1 August 2025, and the latest update posted on 29 September 2026 [52]. The registered regimen comprised mesalamine 1 g three times daily plus ALA 600 mg/day or placebo for 3 months. No results were posted in the registry, and the targeted literature update did not identify a corresponding efficacy publication. Completion is an administrative study status, not evidence of benefit. Future evaluation should include objective inflammatory and endoscopic outcomes alongside symptoms [4].

Preclinical combination studies do not establish a general benefit from adding ALA to another treatment. Taner et al. began oral ALA at 100 mg/kg/day, mesalamine at 50 mg/kg/day, or both 24 h after acetic-acid induction and continued treatment for 14 days [16]. ALA-containing regimens improved selected redox and histological outcomes. For mitochondrial proteins, the reported comparisons support lower dynamin-related protein 1 (DRP1) with the combination versus untreated colitis, while lower mitofusin-2 (MFN2) was significant with mesalamine alone. None of the treatment groups had significantly lower PTEN-induced kinase 1 (PINK1) levels than the untreated colitis group [16]. These protein measurements do not establish restored mitochondrial function or pharmacological synergy. In another acetic-acid model, co-administration with cyclosporine aggravated colonic ulceration, with involvement of a proposed nitric oxide/COX-2/microRNA-210 mechanism [53]. Combination effects therefore require evaluation for each partner drug.

Safety requires the same discipline. Clinical familiarity with ALA in other indications does not establish safety in UC. Severe toxicity has been reported after large overdoses [54], and the European Food Safety Authority concluded that ALA can trigger insulin autoimmune syndrome in genetically susceptible individuals without identifying a risk-free intake threshold [55]. Early UC trials should therefore prespecify adverse-event surveillance, glucose-related risk assessment, and review of concomitant medication.

6.4. Candidate Pharmacodynamic Biomarkers

No biomarker currently identifies an ALA-responsive UC subgroup. Nrf2 activity, lipid-peroxidation products, ferroptosis markers, SCFAs, microbial features, and barrier proteins are plausible pharmacodynamic candidates because each is linked to preclinical observations. None has predictive validation in patients. Their immediate role should therefore be to test whether exposure engages the proposed biology and whether that engagement tracks with clinical or endoscopic improvement.

A useful trial would pair disease-activity outcomes with exposure measurements and prespecified biomarkers. Stool sampling and clinically indicated biopsies could test whether changes in the proposed biology accompany objective improvement. Biomarker findings should remain exploratory until their reproducibility and clinical relevance are established.

6.5. Limitations of the Review

This narrative synthesis is subject to selective retrieval and publication bias and does not provide a formal assessment of study quality. Chemical colitis and simplified cell systems capture only part of human UC, and differences in induction severity, intervention timing, and exposure restrict comparison. Some methods remain unreported or internally inconsistent despite full-text verification, including the FMT timing in Huang et al. [17]. Mechanistic conclusions often rely on concurrent marker changes. Protein abundance does not necessarily demonstrate pathway activity, and fecal-transfer studies do not isolate individual causal mediators. The absence of publicly available clinical efficacy results remains the main barrier to recommending ALA for UC.

7. Conclusions

Free ALA has shown beneficial responses in several experimental colitis and epithelial models. Redox regulation, barrier function, and microbiota changes are supported at different levels, whereas ferroptosis and other pathway-specific explanations remain incompletely validated. Evidence from AL-1 and lipoic-acid-containing materials must be interpreted separately.

Clinical benefit in UC has not been established by publicly available trial results. Further work should define local exposure, test the necessity of proposed mechanisms, and evaluate ALA as an adjunct to standard therapy using objective clinical outcomes.

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