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Review Article

ALPHA-LIPOIC ACID IN TYPE 2 DIABETES MELLITUS: MECHANISMS, CLINICAL BENEFITS, AND IMPLEMENTATION IN THERAPY

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ABSTRACT

Diabetes Mellitus (DM) encompasses a range of metabolic disorders marked by persistent high blood glucose levels. Type 2 Diabetes Mellitus (T2DM), the more common form of the disease is characterized by insulin resistance and partial insulin deficiency. The primary contributors to mortality and morbidity in diabetes are its vascular complications. Alpha-Lipoic Acid (ALA) is an antioxidant derived from caprylic acid and synthesized within the mitochondria. Extensive research shows that ALA aids in preventing and treating Diabetic Neuropathy (DN), lowers the risk of diabetes in at-risk individuals and is also beneficial for those with impaired glucose tolerance. Therefore, this review article aims to explore the different aspects of ALA and its beneficial effects on individuals with T2DM. A range of articles from databases such as Springer, Wiley, Web of Science, PubMed, Google Scholar, SCOPUS, Embase and Cochrane were examined. References from these articles were also analysed to broaden the search for pertinent reviews. Administering ALA in T2DM was found to have beneficial effects like anti-oxidant, anti-inflammatory, enhance glucose uptake, prevents diabetic neuropathy, neuroprotective, anti-obesity, cardio-protective, reno-protective, prevent diabetic retinopathy, anti-aging and improve metabolic parameters in Polycystic Ovary Syndrome (PCOS). Incorporating ALA into a comprehensive treatment plan, combined with lifestyle changes and standard therapies could improve patient outcome and enhance the quality of life for those managing T2DM and related conditions.

Keywords: Alpha Lipoic Acid, Type 2 Diabetes Mellitus, ALA, Diabetic Neuropathy, Antioxidant, Anti-inflammatory

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INTRODUCTION

Diabetes mellitus (DM) encompasses a range of metabolic disorders marked by persistent high blood glucose levels which may stem from problems with insulin production, insulin action, or both. The main categories of diabetes include type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM). T1DM is an autoimmune disorder in which the body's immune system targets and destroys the insulin-producing beta cells in the pancreas, resulting in no insulin production. T2DM is the most common type, typically arising in adults but increasingly being identified in younger individuals. It is characterized by insulin resistance and a partial deficiency of insulin often associated with obesity, physical inactivity, and various environmental and genetic factors [1]. GDM develops during pregnancy, resulting in higher blood sugar levels that can affect both the mother and the baby. Insulin is a polypeptide hormone produced by the beta cells in the islets of Langerhans in the pancreas. Its primary roles include regulating blood glucose levels, facilitating the assimilation of glucose, and promoting its utilization within the body [2].

DM is recognized as one of the most rapidly increasing and prevalent diseases globally [3]. By 2045, it is estimated to impact approximately 693 million adults [4]. The primary contributors to mortality and morbidity in diabetes are its vascular complications, which encompass both macrovascular and microvascular issues [5]. The disease also imposes a substantial economic burden on both developing and developed nations [6].

Diabetic neuropathy (DN) is a prevalent complication of T2DM and presents in various forms, including symmetric sensorimotor neuropathy, autonomic neuropathy, mononeuropathy, mononeuritis multiplex, polyradiculopathy, and plexopathy [7]. Diabetic Symmetric polyneuropathy (DSPN) is estimated to affect 29% of individuals with T1DM and 35% of those with T2DM in Asia [8], and approximately 30% of the global population with diabetes [9].

Alpha-lipoic acid (ALA) is an antioxidant derived from caprylic acid and synthesized within the mitochondria. Studies have shown that nutritional supplementation with ALA may be an effective preventive strategy for managing diabetic complications [10]. Research has shown that ALA enhances nitric oxide-mediated endothelium-dependent vasodilation in diabetic patients and improves microcirculation in those with DSPN [11].

In the 1950s, experimental studies demonstrated that ALA, a naturally occurring compound, could prevent the onset of alloxan diabetes in rats [12]. The use of oral ALA for DN was first reported in the 1960s [13]. Klein et al in 1975 documented the treatment of 100 patients with *DN* using oral ALA [14]. ALA is a powerful antioxidant utilized in the treatment of DN because it helps prevent neuronal lipid peroxidation [15]. It was found to have anti-diabetic effect which is linked to its partial inhibition of islet inflammation. Its anti-inflammatory properties are attributed to its capacity to scavenge oxygen radicals and inhibit nitric oxide production [16].

There is strong research evidence indicating that ALA has beneficial effects in diabetes, especially in the prevention and treatment of DN. It may also aid in preventing diabetes in individuals at risk. The current expert opinions suggest that ALA could be beneficial for patients with impaired glucose tolerance [17]. Therefore, this review article aims to explore the different aspects of ALA and its beneficial effects on individuals with T2DM.

METHODS

A range of articles from databases such as Springer, Wiley, Web of Science, PubMed, Google Scholar, SCOPUS, Embase, and Cochrane were examined. References from these articles were also analyzed to broaden the search for pertinent reviews. Each article was reviewed in detail about the significance of their findings.

RESULTS AND DISCUSSION

Pathophysiology of type 2 diabetes mellitus

T2DM may remain undetected in its early stages due to its gradual progression and often asymptomatic nature, with symptoms sometimes manifesting only as mild hyperglycemia. More noticeable signs such as increased thirst, weight loss, blurred vision, and impaired growth typically emerge later in the disease's course. The development of T2DM is frequently associated with lifestyle issues such as poor diet, aging, physical inactivity, a family history of diabetes, obesity, previous gestational diabetes in women, and related health conditions such as atherosclerosis, hypertension, and dyslipidemia [18].

The pathophysiology of T2DM is characterized by both insulin deficiency and insulin resistance. These conditions are associated with elevated inflammatory cytokines in the plasma and high fatty acid levels, which impair glucose transport into target cells, increase fat breakdown, and boost hepatic glucose production. This results in hyperglycemia, which is further exacerbated by excessive glucagon secretion from α-cells and insufficient insulin production from β-cells of pancreas [19].

Understanding of T2DM has progressed from identifying a combination of pancreatic β-cell dysfunction with impaired insulin secretion and insulin resistance (IR) to a more comprehensive model that now includes hepatic gluconeogenesis. Recently, the "ominous octet" framework has been introduced, adding factors such as incretin deficiencies, abnormal adipocyte metabolism, increased renal glucose reabsorption, elevated glucagon levels, neurotransmitter imbalances, and disrupted central appetite control. Further refinement came with the "dirty dozen" concept, which incorporates additional elements such as dopamine, vitamin D, testosterone, and the renin-angiotensin system thereby offering a more nuanced view of the disease [20].

Structure, synthesis & bioavailability of ALA

ALA plays a crucial role in several enzymatic processes. ALA exists in both R- and S-enantiomeric forms. However, only R-lipoic acid is attached to conserved lysine residues through an amide linkage, making this isoform crucial as a cofactor in biological systems [21]. ALA functions as a cofactor for the activities of pyruvate dehydrogenase and α-keto-glutarate dehydrogenase. It is also essential for the oxidative decarboxylation of pyruvate to acetyl-CoA, a crucial step connecting glycolysis to the citric acid cycle [22]. Overall bioavailability of ALA can vary depending on whether it is consumed as a free acid or a salt, and whether it is taken with or without a meal [23,24]. Pharmacokinetically, ALA has an oral bioavailability of about 30% due to its brief half-life, significant pre-systemic elimination, and hepatic first-pass metabolism [25].

Dietary intake of ALA

ALA can be found in common dietary sources such as muscle meats, kidney, heart, and liver, while smaller quantities are present in fruits and vegetables [26-28]. Although ALA can be found in normal dietary sources, significant amounts are unlikely to be consumed in a typical diet. Instead, dietary supplements which usually contain between 50 and 600 mg of ALA serve as the primary sources. Most information about its bioavailability comes from studies involving these supplements.

BENEFICIAL ACTIONS OF ALA IN DIABETES

Anti-oxidant effect

The oxidized form of lipoic acid (LA) and its reduced form (DHLA) form a powerful redox pair. Studies have shown that the LA/DHLA redox couple has a redox potential of −320 mV, compared to −240 mV for the GSH/oxidized glutathione (GSH/GSSG) pair. This disparity indicates that DHLA may provide enhanced protection against oxidative damage when compared to GSH. As a result, the LA/DHLA couple has been referred to as the "universal antioxidant" [29].

Unlike glutathione (GSH), where only the reduced form acts as an antioxidant, both the oxidized and reduced forms of LA are effective antioxidants. Their functions include neutralizing Reactive Oxygen Species (ROS), regenerating both exogenous and endogenous antioxidants such as vitamins C and E and GSH binding metal ions, repairing oxidized proteins, regulating gene transcription, and inhibiting the activation of Nuclear Factor-kappa B (NF-kB) [30].

Anti-inflammatory effect

Reactive Oxygen Species (ROS) and reactive nitrogen species are byproducts of normal cellular metabolism, generated through processes such as NADPH-oxidase, myeloperoxidase, and nitric oxide synthase. Excessive production of these reactive species can lead to damage within the host [10]. Moreover, reactive oxygen and nitrogen species (RONS) initiate oxidative stress by acting as signaling messengers in various cell death pathways, including apoptosis, necrosis, and autophagy [31]. Free radicals can also generate secondary radicals, which contribute to oxidative stress and toxicity [32]. Therefore, it is essential to maintain redox homeostasis to prevent such damage. Redox homeostasis is upheld by an internal defense system that includes enzymes such as superoxide dismutase, catalase, and glutathione peroxidase as well as molecules such as ascorbate, glutathione, flavonoids, tocopherol, carotenoids, and ubiquinol. ALA is produced within the human body to act as an antioxidant, protecting cells from damage and assisting in the regeneration of other antioxidants such as vitamins C and E [33]. In addition, ALA may lower blood levels of various inflammatory markers such as IL-6 and ICAM-1. The recommended dosage of ALA is 300–600 mg daily and no issues have been reported in individuals taking 600 mg per day for up to 7 months [34].

Enhance glucose uptake

ALA enhances the recruitment of glucose transport protein 4 (GLUT4) from its storage site in the Golgi apparatus to the cell membrane, thereby increasing glucose uptake by boosting the number of GLUT4 transporters on the cell surface. Evidence from cell culture studies supports the involvement of insulin-mediated PI3K activity in ALA-induced glucose uptake, with this effect being sensitive to wortmannin, a PI3K inhibitor. However, further direct and relevant evidence is needed to confirm the role of GLUT4 translocation in improving glucose disposal with ALA administration [35,36].

Diabetic neuropathy

When ROS accumulate beyond the capacity of these endogenous defenses, oxidative stress increases. This elevated oxidative stress has been linked to the development of painful neuropathies in diabetes [37].

In 2012, Mijnhout carried out a meta-analysis that analyzed four studies with an overall participant count of 653 patients. The findings revealed that intravenous administration of ALA at 600 mg daily for 3 weeks significantly reduced the total symptom score (TSS). However, the analysis did not assess the impact of oral ALA [38]. Another related study indicated that intravenous ALA administration for 2 to 4 weeks led to more favorable results in nerve conduction studies (NCS) and neuropathic symptoms [39]. Liu et al from China reported the treatment of 50 type 2 diabetic patients who had DN with ALA 600 mg given in 250 normal saline once daily for two weeks. The findings were compared with a placebo group which included 43 type 2 diabetic patients who had DN and received radix salviae infusion. ALA treatment was associated with an improvement rate of 90% which was considerably higher than the placebo group [40].

ALA and coenzyme Q10 assist in preventing the degeneration of dorsal root ganglion (DRG) neurons by modulating the expression of caspase-3 and uncoupling protein 2 (UCP2). This regulation promotes ATP production and mitigates the changes in DRG neurons induced by DN [41].

Neuroprotective

ALA was known to exert neuroprotective property because of its role as an antioxidant. Administration of ALA (20 mg/kg) through the jugular vein helps protect the nervous system by reducing mortality, neurological deficits, and infarction while enhancing neurogenesis

and brain cell metabolism [42]. In addition, ALA promotes the M2 phenotype in microglia; regulates the levels of pro-inflammatory cytokines such as IL-6, IL-1, IL-10, and tumor necrosis factor (TNF); and inhibits NF-κB, a key transcription factor involved in inflammatory responses [43]. ALA also demonstrated neuroprotective effects against glucose fluctuations by enhancing the expression of TrkA/p75NTR and activating the p-AKT/AKT pathways [44].

Anti-obesity

A clinical study has found that ALA supplementation can lead to reductions in body weight and body mass index (BMI) [45]. A dosage of 1800 mg/day of ALA resulted in modest weight loss among obese individuals [46]. ALA therapy elicited a rapid clinical response in obese and pre-obese patients by reducing plasma levels of pro-inflammatory cytokines. Notably, there was a significant decrease in circulating TNF levels following treatment [47]. In addition, given the central role of IL-6 in mediating pro-inflammatory pathways, the significant reduction in circulating IL-6 levels post-treatment is a crucial factor in the clinical improvement of pre-obese and obese patients and in the prevention of chronic diseases [48,49].

Cardio-protective

It has been found that macrophages, smooth muscle cells, and ROS scavenger receptors on monocytes excessively ingest oxidized LDL, leading to lipid buildup and the formation of atherosclerotic plaques. Increased oxidative stress and inflammation generate hydroxyl radicals, peroxides, and superoxide within the endothelium which accelerate the progression of cardiovascular disease. DHLA is noted for its ability to modulate blood lipids, protect against LDL oxidation, and influence hypertension (HTN). This suggests that ALA could potentially serve as a protective agent against cardiovascular diseases (CVDs) [27].

Several studies indicate that infusing irbesartan and ALA in patients with metabolic syndrome reduces pro-inflammatory markers and improves endothelial function, both of which are involved in the development of atherosclerosis [50].

Reno-protective

T2DM is the major cause of chronic kidney disease (CKD). Diabetic kidney disease (DKD) is marked by reduced glomerular filtration, proteinuria, and renal fibrosis [51]. It is well established that mitochondrial dysfunction plays a role in DKD, making the mitochondrion a key target for addressing and combating this condition [52,53,54]. Hypoxia, ROS, and oxidative stress can lead to significant kidney damage [55]. Lipoamide, a derivative of ALA, has been shown to inhibit kidney fibrosis in diabetes by improving mitochondrial function and regulating the expression of the transcription factor retinal X receptor alpha [56].

Administering ALA (600 mg/day) alongside antioxidants such as *α-tocopherol* or vitamin E (300–1000 mg/day) and *N-acetylcysteine* (600–1200 mg/day) may benefit dialysis patients by reducing elevated oxidative stress [57,58,59]. In DN, TGFβ1 interacts with MAPK to increase fibronectin in mesangial cells. ALA alleviates proteinuria by lowering TGFβ1 and fibronectin levels [60]. It was found that ALA protects kidney against damage due to iron overload by inhibiting p38 MAPK signaling pathways [61]. By targeting NF-κB and reducing the release of inflammatory cytokines, it has been shown that ALA scavenges oxygen radicals thereby mitigating inflammation [62]. Malondialdehyde (MDA), a byproduct of lipid peroxidation, is widely used as an indicator of free radicals and oxidative stress [63].

Research has demonstrated that pretreatment with ALA reduces MDA levels and alleviates renal oxidative stress [64]. In addition, ALA has been believed to activate insulin signaling pathways to address DM and has been shown to prevent cardiometabolic disorders and renal dysfunction induced by high fructose [29,65]. However, it has also been reported that ALA may only reduce proteinuria and oxidative stress without significantly slowing the progression of diabetic renal failure [66].

Diabetic retinopathy

In developed countries, the most common and prevalent cause of blindness is due to diabetic retinopathy (DR), especially among working-age adults. Within 5 years of diagnosis, 25% of patients with T1DM might show signs of DR [67]. ALA helps prevent DR by inhibiting O-linked β-N-acetylglucosamine transferase and NF-kB activity as well as reducing oxidative stress. It also activates nuclear factor erythroid-2-related factor 2 and AMP-activated protein kinase in retinal ganglion cells. Clinical trials in pre-retinopathic diabetic patients have demonstrated that ALA combined with *Genistein* and vitamins can protect retinal cells and reduce inflammation in diabetic patients [68].

Polycystic ovarian syndrome

In polycystic ovary syndrome (PCOS), ALA also reduces oxidative damage and insulin resistance. In a study involving 90 obese patients with PCOS, the combination of ALA (400 mg/day) and myo-inositol (1 mg/day) improved hormonal and metabolic parameters including insulin sensitivity [69]. Integrative administration of ALA (400 mg/day) enhances metabolic function in all PCOS patients, particularly benefiting those at high risk for non-alcoholic fatty liver disease (NAFLD) and predisposed to diabetes [70].

Anti-aging

Oxidative stress was found to be the process involved in cellular aging and aging-related organ dysfunction. Antioxidants might decrease the likelihood of certain heart conditions and may also offer anti-aging benefits. ALA can inhibit aging pathways in pancreatic islet cells through its antioxidant properties [71].

SIDE EFFECTS OF ALA

Hirata disease, also known as insulin autoimmune syndrome (IAS), is characterized by high insulin levels and the presence of anti-insulin autoantibodies. This rare form of autoimmune hypoglycemia is triggered by sulfhydryl-containing medications that stimulate the production of insulin autoantibodies and recent studies have found that ALA as one of the causative factors of IAS. Consequently, caution is advised when considering ALA supplementation given its association with this condition [72].

Previous studies have shown that doses of up to 2400 mg for adults are well tolerated without any adverse effects. However, higher doses do not provide any additional nutritional or therapeutic benefits and hence should not be recommended [73]. Daily oral supplementation of 600 mg of ALA during pregnancy has not been associated with adverse effects for either mothers or newborns, but it is strongly advised to use it under medical supervision [74].

Studies on primates have shown that excessively high doses of ALA can cause hepatic necrosis, suggesting that very high intravenous doses may lead to toxicity [75]. The most common side effect of ALA is gastrointestinal issues. Allergic reactions such as rashes, hives, and itching can occur with oral ALA intake. Patients may also experience vomiting, diarrhea, and vertigo [57].

CONCLUSION

This systematic review of ALA has highlighted its various beneficial and therapeutic effects in T2DM. ALA represents a multifaceted therapeutic agent with substantial promise for managing T2DM and its related complications. Fig. 1 depicts various mechanisms by which ALA exerts its beneficial effects in T2DM. Its potent antioxidant properties are pivotal in neutralizing ROS, regenerating other antioxidants, and repairing oxidized proteins thereby mitigating oxidative stress which is a significant contributor to T2DM pathology. By chelating metal ions and inhibiting NF-kB, ALA not only alleviates oxidative damage but also reduces inflammation addressing critical pathways involved in diabetic complications. ALA's anti-inflammatory effects are particularly noteworthy, as it reduces key inflammatory markers such as IL-6 and ICAM-1, further supporting its role in managing chronic inflammation

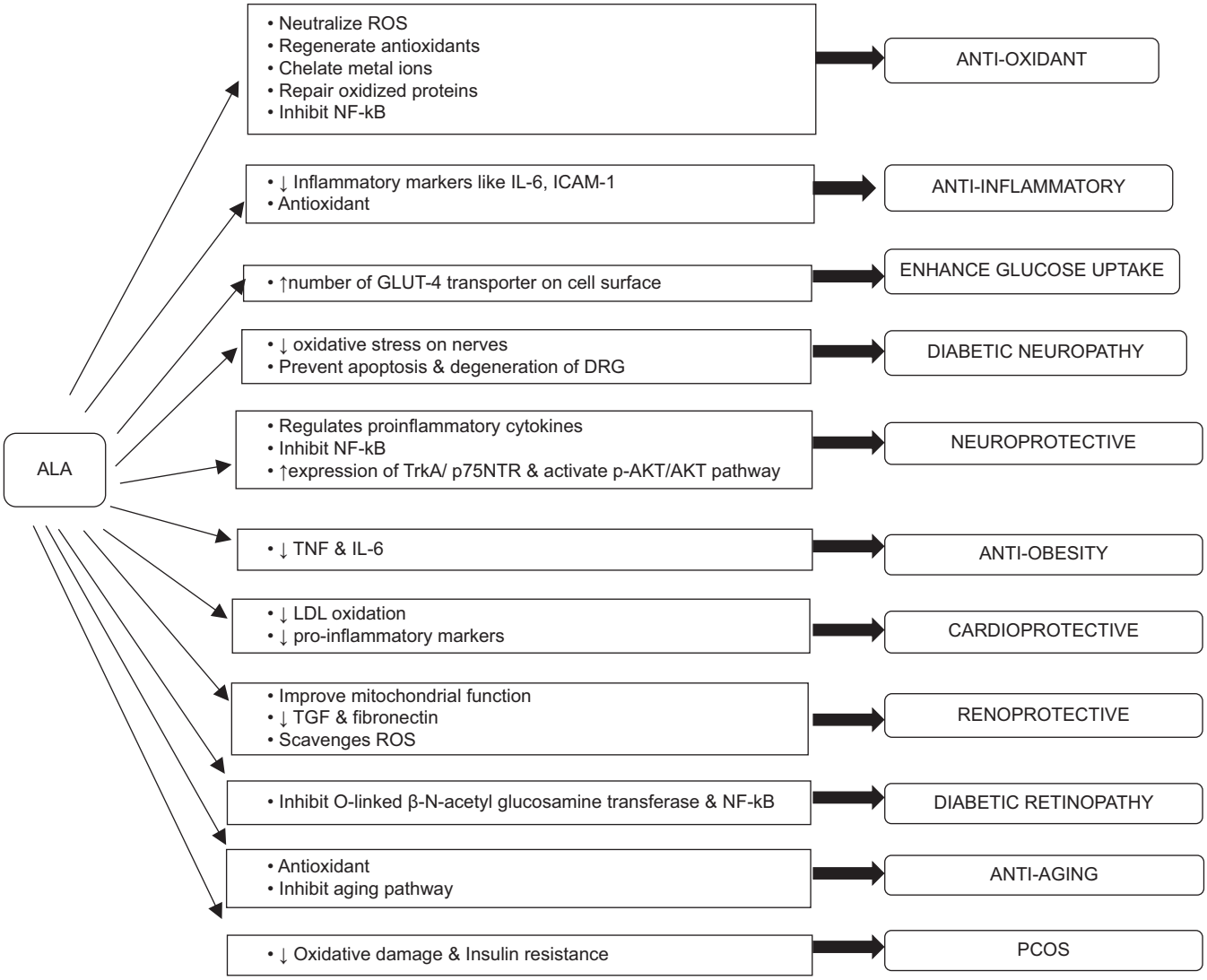

Fig. 1: Summary of beneficial actions of alpha-lipoic acid in type 2 diabetes mellitus

associated with T2DM. The enhancement of glucose uptake through increased GLUT-4 transporter expression on the cell surface offers a direct benefit for glycemic control, making ALA a valuable adjunct in diabetes management.

In the realm of DN, ALA has demonstrated efficacy in reducing oxidative stress on nerves, preventing apoptosis, and preserving the integrity of DRG. Its neuroprotective properties are bolstered by its ability to regulate proinflammatory cytokines, inhibit NF-kB, and enhance signaling pathways such as TrkA/p75NTR and the p-AKT/AKT pathway all of which contribute to nerve health and function.

ALA also shows promise in addressing obesity-related concerns by reducing TNF and IL-6, while its cardioprotective and reno-protective effects, evidenced by decreased LDL oxidation, reduced pro-inflammatory markers, and improved mitochondrial function highlight its broader therapeutic potential. Furthermore, its role in mitigating DR through inhibition of specific glycosylation processes and NF-kB underscores its importance in preventing long-term complications. In addition to these benefits, ALA has demonstrated efficacy in reducing oxidative damage and insulin resistance in PCOS, suggesting a versatile role in metabolic disorders beyond diabetes alone. Its anti-aging properties further complement its therapeutic profile.

While the evidence supporting ALA's benefits is robust, continued research is essential to fully establish its efficacy, optimal dosing, and long-term safety. Future studies should focus on validating these effects through large-scale, well-designed clinical trials to confirm ALA's role as a valuable adjunct in T2DM treatment regimens. Integrating ALA into a multifaceted approach, alongside lifestyle modifications and conventional therapies may enhance patient outcomes and improve quality of life for individuals managing T2DM and its associated conditions.

AUTHOR CONTRIBUTION

All authors contributed to the study's conception and design. B. Dharani, Suba.A, and Stephy Sebastian were responsible for data collection and analysis. The first draft of the manuscript was written by B. Dharani and Stephy Sebastian, with Suba.A helping to gather articles. Each author reviewed previous drafts, offered feedback, and approved the final version.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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