

The mechanism of action of alpha-lipoic acid in the treatment of type 2 diabetes and its complications

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Abstract. Type 2 diabetes mellitus is now one of the metabolic disorders in the world, Oxidative stress and chronic inflammation are the reasons for serious diseases such as insulin resistance and peripheral neuropathy, and the existing drugs are unable to prevent these diseases at the level of pathology. Alpha-lipoic acid is a very effective multi-functional antioxidant and has shown some good results in diabetes research, First, we will introduce the main mechanisms by which alpha-lipoic acid has antioxidant and anti-stress effects; there are many reasons for its good antioxidant and anti-aging properties, such as directly scavenging free radicals and reactive oxygen species (ROS), chelating metal ions, repairing oxidative damage, regenerating endogenous antioxidants, modulating signaling pathways, etc. It is non-inflammatory and may lower the amount of pro-inflammatory cytokines in the body by suppressing inflammation. It also reveals that there are some neuroprotective and symptomatic-reducing effects on diabetic peripheral neuropathy, By comparing the old way of treating diseases, this paper finds that alpha-lipoic acid has two advantages in targeted treatment and blocking the course of disease, However, its clinical dosage and safety over long periods have not been confirmed yet. In order to learn how to use α -lipoic acid for preventing and treating complications of type 2 diabetes better, this paper will explore related research at the molecular level and provide a reference for the development of new drugs.

Keywords: α -lipoic acid, type 2 diabetes mellitus, oxidative stress response, anti-inflammatory, insulin resistance.

1. Introduction

Alpha-lipoic acid (ALA) is one of the nutrients in broccoli and spinach, and it can also be obtained from offal of animals, It can be produced by enzymatic reactions of capric acid and cysteine in the mitochondria of plants and animals, Chemically speaking, [1] the disulfide pentacycle of ALA can be reduced to dihydrolycine (DHLA), and the oxidation-reduction electrode potential of ALA and DHLA is -0.32 V ; thus, both the glutathione (GSH)/oxidized glutathione (GSSG) ratio (-0.24 V) and the cystine/cysteine ratio (-0.22 V) have good antioxidant protection properties. ALA is needed for some complexes of mitochondrial polyenzymes, such as pyruvate dehydrogenase (PDH), α -ketoglutarate dehydrogenase (KGDH) and flavin adenine dinucleotide (FAD), and it can directly affect the power output of cells by changing the tricarboxylic acid cycle (TCA cycle) [2], The two enantiomers of ALA are R and S, The R subtype of the enzyme in the electron transport chain oxidases is required for its function to transfer electrons from lysine. R-ALA has a greater biological effect than S-ALA in some metabolic pathways, Type 2 diabetes mellitus (T2DM) is one of the common endocrine disorders, and at present, it is one of the leading chronic diseases among middle-aged and elderly people in China, with an increasing annual incidence and considerable impact on the quality of life, More serious oxidative stress and inflammation in diabetic patients are associated with increased insulin resistance, and by reducing this stress and inflammation, one can improve it. Therefore, antioxidant and anti-inflammatory therapy are essential parts of the treatment for people with Type 2 diabetes; they can reduce damage to the endothelial cells caused by oxidative stress and help control blood sugar levels and improve function of pancreatic islet cells, Review of the Physicochemical Properties and Antioxidant and Anti-inflammatory Effects of ALA Based on Current Research at Home and Abroad, This paper will determine how ALA is transported in all organisms and provide a scientific basis for its application in clinical practice and the development of allopathic drugs.

2. Mechanism of alpha-lipoic acid in combating oxidative stress

Reactive Oxygen Species (ROS) are small molecules in the body that can cause damage to vascular cells and thus promote cell growth. After caloric intake, the use of oxygen by cells produces byproducts in the form of high-energy oxygen molecules. The above are all free radicals, which are reactive oxygen species. Free radicals can cause damage to human tissues and cells, which is called oxidative stress; it refers to the stress on the body caused by oxygen use; insulin resistance arises from oxidative stress. As a result of the increase in free fatty acids (FFAs), more highly reactive species, such as ROS and RNS, are formed; these species can cause an oxidative stress mechanism, and a prolonged state of imbalance between the production of highly reactive molecules and antioxidant capacity is known as oxidative stress, which leads to tissue injury. Reactive molecules can directly damage DNA, proteins and lipids, and at the same time, they can act as chemical signals to activate many stress-response signalling pathways in cells that are involved in insulin resistance and impaired beta-cell function. beta-cells are also susceptible to oxidative stress, and due to the relatively low level of antioxidant enzymes, they are particularly vulnerable to reactive oxygen species (ROS). ROS can directly damage pancreatic beta-cells, induce apoptosis of beta-cells, impair beta-cell function through changes in insulin signalling, etc. Damaged beta-cells decrease the secretion of insulin, delay the increase in insulin after eating, and cause fluctuations in blood sugar; they are unable to respond to the sudden rise in blood sugar after a meal effectively and lead to more damage of the cells, as shown in Figure 1.

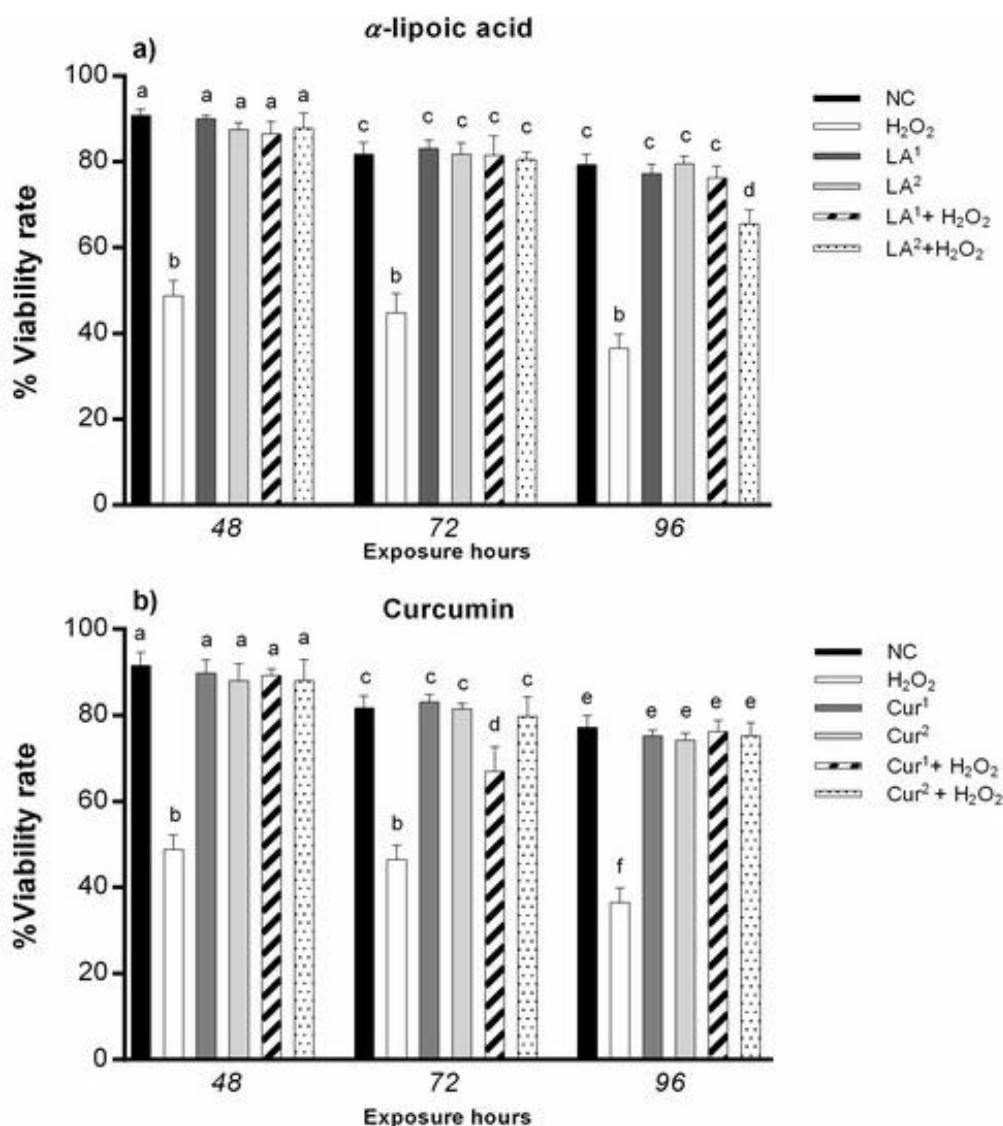


Fig. 1 The Antioxidant Stress Mechanism of α -Lipoic Acid.

2.1. Directly eliminate free radicals and reactive oxygen species

ALA is a reducing agent; thus, it can reduce the production of reactive oxygen species (ROS) such as hydroxyl radicals, nitric oxide, hypochlorous acid, etc., through a redox reaction and protect cells from oxidative damage. Malondialdehyde (MDA) is highly reactive and among the most electrophilic agents that cause cell injury by forming covalent protein adducts, which are known as advanced lipid oxidation end products (ALE) and are similar to advanced glycation end products (AGE). MDA is produced in the process; it can be used as an indicator of the level of oxidative stress in living things and is one of the important biomarkers for antioxidant capacity of tissue cells. Zhang and others [3] have shown that adding ALA to the diet of sheep can reduce the level of MDA in their blood; therefore, it is believed that ALA enhances the antioxidant capacity of sheep by inhibiting or eliminating ROS generated through lipid peroxidation and oxidative stress to protect tissues and cells from damage caused by oxidation. Sun Jiayi et al. [4] have shown in studies that adding 0.1 mmol/L ALA can improve the quality of Hu sheep semen under low-temperature storage conditions, enhance sperm motility and viability, inhibit the generation of ROS and MDA in semen effectively, reduce oxidative stress damage, etc.

2.2. Chelated metal ion

Many transition metal ions in living organisms, such as Fe^{2+} , Cu^{2+} and Zn^{2+} , have the property of catalyzing the decomposition of hydrogen peroxide to produce very toxic hydroxyl radicals ($\text{OH}\cdot$) that cause oxidative damage to tissues. ALA is a good chelator that can form stable complexes with Fe^{2+} , Cu^{2+} , Mn^{2+} , Zn^{2+} , Pb^{2+} and other ions to reduce the production of free radicals and maintain the body's antioxidant status. Many animal studies have shown that ALA can reduce the harm of neurotoxicity, immunotoxicity and male reproductive toxicity caused by the combined exposure of lead and zinc oxide nanoparticles. It can reduce damage from oxidative stress in the nervous system, immune system and other target organs caused by the combination of these factors, restore antioxidant homeostasis of the body, etc. ALA can also reduce the concentration of lead and zinc in rat blood and thus reduce the remaining amount of heavy metals and nanoparticles in the body's circulatory system. ALA has many protective functions, that is to say, it can quench free radicals and regulate antioxidant enzymes; at the same time, it also has weak metal-ion chelating capacity to weakly bind with free metal ions and reduce their bioavailability and tissue toxicity, thus protecting all organs from damage caused by complex exposure [5].

2.3. Repair long-standing oxidative damage

ALA can repair the long-term damage caused by free radicals in the body. Proteins are biomolecules that have relatively weak renewal and regeneration abilities; therefore, the repair of oxidative damage is a serious problem, and some specific methionine residues can be inactivated by oxidation, and the repair of these residues is carried out by peptide-methionine fumarate reductase (PMSR). At the same time, antioxidant ALA is also added to PMSR at this time of repair to reduce PMSR and thus restore the methionine residue. ALA has the physicochemical properties of both lipophilic and hydrophilic substances, so it can pass through biological membranes and spread extensively in the tissues and cells. Therefore, it will also be able to inhibit oxidative damage in different parts of the cell. ALA has the characteristic of being able to maintain the normal structure and function of cells and reduce damage caused by oxidation.

In the previous studies, under oxidative stress caused by paraquat exposure in fattening pigs, ALA has shown that it can reduce damage to the intestinal wall, maintain the structure of the intestine and possess some enhancing and repairing functions for damaged digestive function in the intestine [6]. ALA has good repair and protection functions for DNA damaged by oxidative stress, can maintain the stability of the genome, and through random amplified polymorphic DNA-polymerase chain reaction (RAPD-PCR), it has been found in studies [7] that at an ALA concentration of 200 $\mu\text{mol/L}$, there is a significant antioxidant protective effect on anti-oxidative DNA damage in human amniotic cells.

2.4. Regenerate endogenous antioxidants

Research has found that both ALA and its reduced metabolite DHLA are involved in the cycle of antioxidant system reconstruction in the body. Upon entering the cell, ALA is quickly converted into DHLA and then widely distributed in many parts of the body. A redox-coupling reaction can reduce the oxidation state of both substances; that is to say, the oxidized form of vitamin C and vitamin E will be converted into their reduced, active states, and thus, the antioxidant function can be recovered or maintained. The reduction of excess free radicals and reactive oxygen species in the body is carried out by several natural antioxidant substances. These are all involved in this work jointly and cooperatively; among them, Vitamin C, glutathione (GSH), Vitamin E, coenzyme Q, etc., are included. Glutathione is a thiopeptide composed of glutamate, alanine and glycine, and its production depends on the supply of its precursor (alanine). The ALA/DHLA pathway is used to produce homopurine and enhance the supply of substrates by means of gene expression [8]. DHLA can reduce the oxidation of coenzyme Q10, repair mitochondrial oxidative damage, maintain the smooth operation of energy metabolism and antioxidant function [9]. Experiments on human amniotic cells [10] have shown that ALA can repair oxidative damage to DNA and is protective in the presence of the repair ability of endogenous antioxidant enzymes.

3. Mechanism of Anti-inflammatory Effects of Alpha-Lipoic Acid

Alpha-lipoic acid is able to inhibit the activation of the main inflammatory signal pathway and thus stop the spread of inflammation. The first transcription factor of chronic inflammation in diabetes is NF- κ B. High glucose or lipotoxic conditions can activate the NF-kappaB pathway, which then enters the nucleus to bind to its target genes and increase the expression of adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) and inflammatory factors; therefore, it may damage the vascular endothelium and promote the development of atherosclerosis [11].

Research has shown that ALA can reduce nitric oxide stress and decrease the activity of MAPK and NF- κ B by regulating the transcription and expression of genes related to inflammation. ALA can also inhibit the signalling of the high-mobility group protein B1/NF-kappaB pathway, change the polarisation of macrophages, and thus reduce the spread of inflammation. ALA reduces the expression of Toll-like receptor 4 (TLR4) and NOD-like receptor protein 3 (NLRP3) inflammatory signals in diabetic nephropathy by inhibiting the expression of Notch2 protein; it is likely that by reducing the release of inflammatory factors, it can alleviate damage to kidney tissue and fibrosis [12]. ALA can also lower the level of pro-inflammatory factors in the blood and protect the kidneys from damage by suppressing the expression of phosphorylated NF- κ B in the kidney of a type 1 diabetes rat model [13]. The anti-inflammatory effect of α -lipoic acid on inhibiting the production of inflammatory mediators is only manifested after it has achieved its anti-diabetic and anti-inflammatory effects. Due to diabetes, there is an increase in the amount of pro-inflammatory factors released by the body's inflammatory cells, such as tumour necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β) and interleukin-6 (IL-6). These factors can directly harm the pancreatic beta cells, reduce the secretion of insulin, increase insulin resistance, and thus form a vicious cycle of inflammation and metabolic dysfunction [14]. ALA can reduce the production and release of the above pro-inflammatory factors by regulating the inflammatory signal transduction pathway. For instance, ALA has been shown to lower the amount of IL-6 and TNF- α and thus reduce inflammation in STZ-induced diabetic rat kidney tissue [12]. According to the model of lipotoxic injury to pancreatic beta-cells, ALA can maintain the normal function of beta-cells by inhibiting the activation of the NF-kappaB pathway and reducing the expression of inflammatory factors such as TNF- α and IL-1 β [14]. ALA can also reduce the amount of lipoprotein-associated phospholipase A2, improve the distribution of lipases in lipoproteins, and inhibit the formation of oxidized low-density lipoprotein; thus, it is also anti-inflammatory [11], as shown in Figure 2.

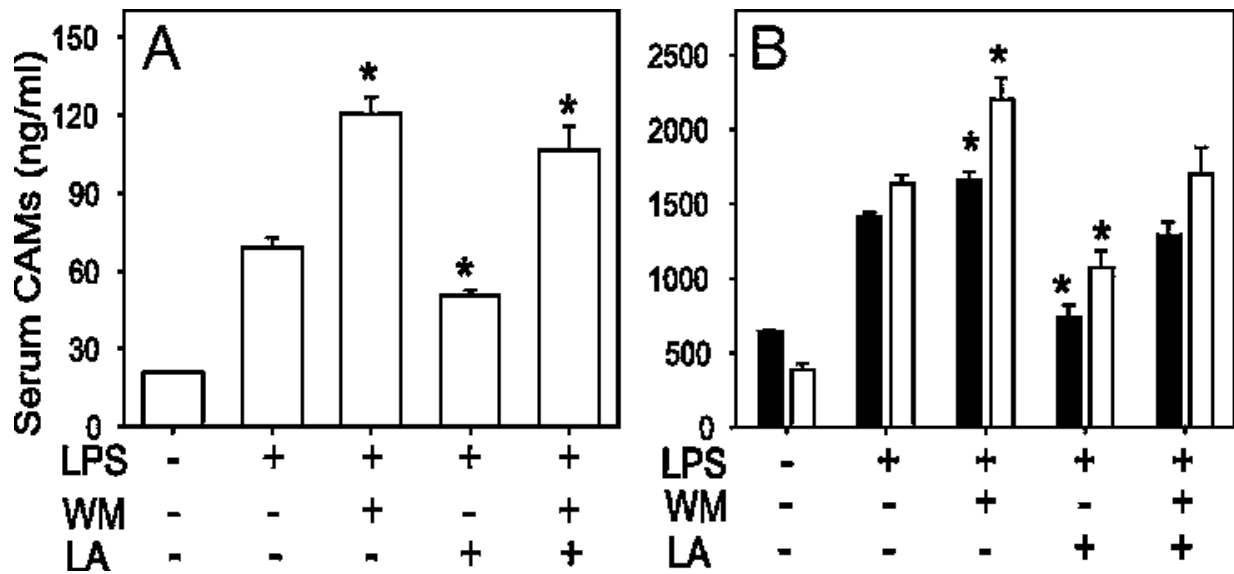


Fig. 2 Schematic diagram of the main inflammatory signalling pathway regulated by alpha-lipoic acid.

Regulate the function and balance of immune cells to enhance the anti-inflammatory effect of α -lipoic acid, In diabetes, there is an abnormal function of immune cells, with increased activity of pro-inflammatory cells such as M1 macrophages and Th17 cells, and impaired function of anti-inflammatory cells such as M2 macrophages and regulatory T cells; thus, there is an imbalance in the inflammatory response, ALA can correct the imbalance by changing the activity and differentiation of immune cells. On the one hand, it can increase the function of M2 macrophages and regulatory T cells to boost the body's anti-inflammatory effect; at the same time, it suppresses the activation of M1 macrophages and Th17 cells and reduces the secretion of pro-inflammatory factors, ALA also inhibits the chemotaxis, adhesion and migration of leukocytes; therefore, it cannot accumulate at the site of inflammation and reduce the severity of tissue injury caused by inflammation [14] , as shown in Figure 3.

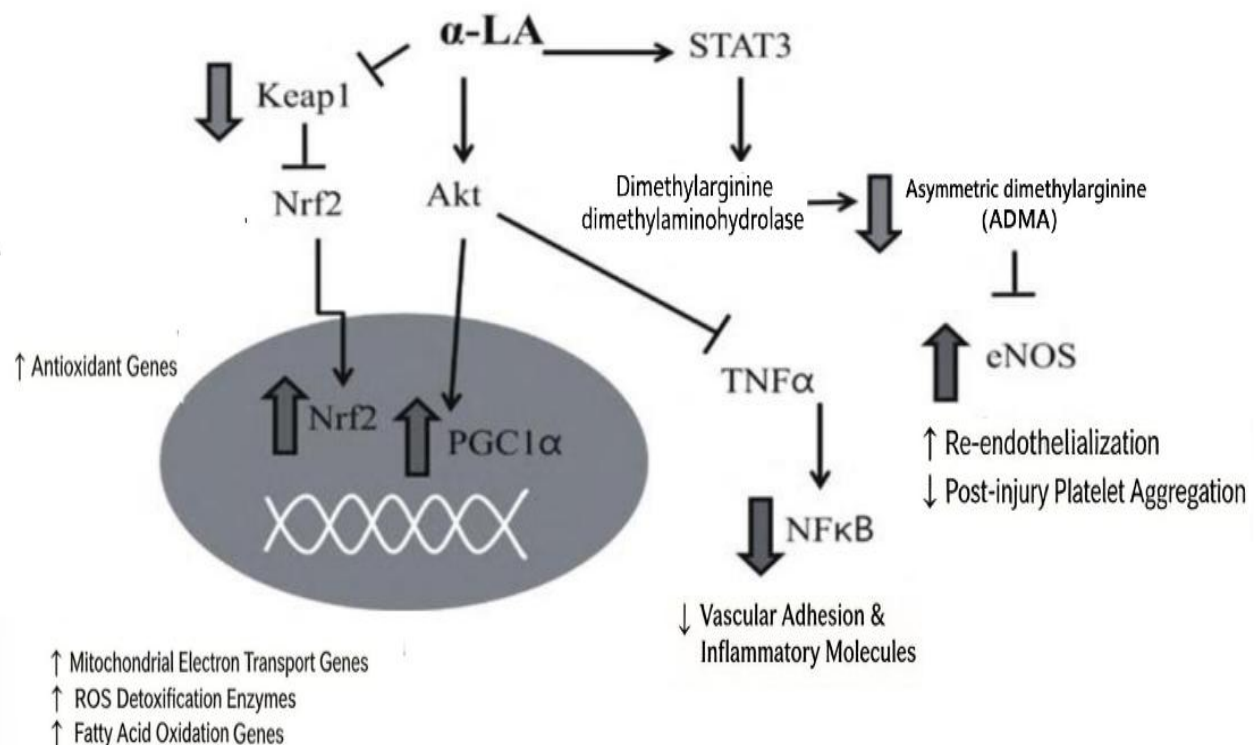


Fig. 3 Several Ways of LA's Good Effect on Vascular Activity

4. Therapeutic Efficacy of Alpha-Lipoic Acid on Complications of Type 2 Diabetes Mellitus

Diabetic neuropathy is one of the typical long-term pathological changes in people with diabetes, which can affect the entire nervous system; among them, diabetic peripheral neuropathy is more frequent, DPN is mainly composed of sensory, motor and autonomic nerves, so it causes sensory and motor disorders, The development of DPN is related to the length of time it has occurred and blood sugar control. Clinical studies have shown that the addition of ALA therapy can help improve the clinical results of early-stage DPN, He Xiaowei and others [15] randomly divided the 144 DPN patients into two groups, gave the control group standard Olmesartan treatment, and had the observation group receive ALA therapy in addition to it and be observed, Overall, the response rate in the treated group after observation was about 86.11%, and this was higher than that in the control group (72.22%); at the same time, the proportion of urinary protein excretion, urinary beta₂-microglobulin and high-sensitivity C-reactive protein (hs-CRP) were all reduced in the treated group. Based on the above results, it can be seen that ALA can reduce inflammation and oxidative stress, decrease the amount of protein in the urine, and maintain normal kidney function, DPN is mainly associated with numbness and tingling in the extremities; it is caused by lipid oxidation in neural tissue, overexpression of the polyol pathway, and reduced nerve conduction velocity, ALA can relieve the sensory symptoms of nerves and improve nerve conduction velocity by inhibiting lipid oxidation in neural tissue, preventing protein glycosylation, enhancing neurotrophic vascular blood flow, and protecting the function of vascular endothelial cells. Clinical trials have found that ALA can improve the treatment effect of diabetic peripheral neuropathy (DPN) when used alone or in combination with drugs such as mecobalamin; it can increase the conduction speed of the peroneal nerve and tibial nerve in the lower limbs, lower high-sensitivity C-reactive protein (hs-CRP), enhance superoxide dismutase (SOD) activity, reduce symptoms such as numbness and tingling in the limbs, etc, A multi-group randomized controlled trial showed that the combination of Mudan Granules, mecobalamin and ALA for the treatment of DPN could further increase the conduction speed of the lower limb peroneal nerve and tibial nerve, reduce inflammation and oxidative stress, and exhibit better clinical results than when only mecobalamin or ALA was used [16], as shown in Figure 4.



Fig. 4 The Mechanism of α -Lipoic Acid in Alleviating Diabetic Peripheral Neuropathy

5. Conclusion

Mechanistic Roles and Clinical Applications of α -lipoic Acid (ALA) in the Prevention and Treatment of Type 2 Diabetes Mellitus and its Complications, Studies have shown that α -lipoic acid has good lipophilicity and hydrophilicity and can thus exert various effects at different levels on type 2 diabetes by reducing oxidative stress and chronic inflammation, Alpha-lipoic acid is a strong antioxidant that can directly neutralize free radicals and other reactive oxygen species (ROS), and it can also chelate metal ions; it can also replenish the body's own antioxidant substances, such as vitamin C, vitamin E and glutathione, to protect beta cells and improve insulin sensitivity. In terms of anti-inflammation, it can inhibit the activation of some important inflammatory signal pathways such as NF-kappaB, MAPK and TLR4/NLRP3; reduce the production of pro-inflammatory substances like TNF-alpha, IL-1beta and IL-6; alter the direction of immune cell differentiation and leukocyte migration; disrupt the positive feedback loop of chronic inflammation in diabetes, etc, Alpha-lipoic acid has been shown in studies to have good neuroprotective and symptomatic improvement effects on diabetic peripheral neuropathy; it can increase nerve conduction velocity and reduce sensory changes, and at the same time, it may also suppress inflammation and fibrosis in kidney tissue to protect kidney function, Therefore, it has received strong experimental support and theoretical support for the overall prevention and treatment of complications related to type 2 diabetes. In short, α -lipoic acid can inhibit the progression of type 2 diabetes and its complications at the level of pathogenesis and is used in combination with conventional glucose-lowering drugs to achieve good effects and has some clinical value, However, the current research has not been able to find an optimal dose and long-term safety; personalised treatment plans for different groups of people and standardised combined protocols with conventional clinical drugs all still need to be confirmed in large-scale, long-term clinical trials, In the future, more studies will be carried out to determine the molecular targets and cross-regulatory mechanisms of alpha-lipoic acid in the regulation of glucose and lipid metabolism, inflammation networks, etc., and its application scope for diabetic macrovascular complications and diabetes-related cognitive impairment will also be expanded. The above efforts will provide more scientific support for the precise clinical application of α -lipoic acid in the treatment of type 2 diabetes.

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