



Research Article

The Potential Role of α -lipoic acid in Diabetes Mellitus

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Abstract:

Diabetes mellitus is a global health, widespread disease, that affects many millions of people all over the world, which consider a serious health problem. Hyperglycemia which consider the main symptoms of diabetes can lead to diabetic complication which is considered the leading cause of morbidity and mortality. Oxidative stress is increased in DM, due to increased level production of oxygen free radicals and decreased the level of the antioxidant defense mechanisms. Natural products are in a particular interest, as they are used to perform important biological functions. Natural compounds possibly to be appropriate alternatives for diabetes therapy. They can decrease the risk factor of many diseases, they can consume in Large amount daily without any side effect as synthetic drugs. Alpha-lipoic acid is a natural substance antioxidant. It is the main cofactor for energy production in the mitochondria. Alpha-lipoic acid has been shown to reduce symptoms of the patient suffering from diabetes. This review article aimed to elucidate the antidiabetic activity of Alpha-lipoic acid as well as showed their merit that makes them ideal for antidiabetic treatment.

Highlights:

1. Diabetes mellitus is a serious metabolic disorders, Hyperglycemia can lead to diabetic complication which is considered the leading cause of morbidity and mortality.
2. Natural compounds possibly to be appropriate alternatives for diabetes therapy. They can decrease the risk factor of many diseases, they can consume in Large daily without any side effect as synthetic drugs.

Alpha-lipoic acid (ALA) is a natural substance antioxidant. It has been shown to reduce symptoms of the patient suffering from diabetes.

Keywords: Alpha-lipoic; Diabetes; Hyperglycaemia

Abbreviation: ALA: Alpha-Lipoic; AMPK: 5' Adenosine Monophosphate-Activated Protein Kinase; CAT: Catalase; DHLA: Dihydrolipoic Acid; DM: Diabetes Mellitus; GPx: Glutathione Peroxidase; GSH: Glutathione; H₂O₂: Hydrogen Peroxide; HMG-CoA Reductase: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; LCAT: Lecithin-Cholesterol Acyltransferase; L-MDA: L-Malonaldehyde; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; PC: Pyruvate Carboxylase; PEPCK: Phosphoenolpyruvate Carboxykinase; STZ: Streptozotocin; TAG: Triacylglycerol

Introduction: Diabetes is the most common endocrine disorder all over the world [1]. Diabetes mellitus (DM) is identified by increased blood

glucose level, lipoprotein disorder, raised the basal metabolic rate, the decrease in the activities of the antioxidant enzymes and high oxidative stress, which prompt damage to pancreatic beta cells [2]. Moreover, DM is a frequent metabolic syndrome initially characterized by loss of glucose homeostasis. The disease is progressive and is associated with a high risk of atherosclerosis [3].

Type I diabetes, also known as Insulin-dependent diabetes mellitus (IDDM), which is identified by absolute insulin deficiency. The main causes of type I diabetes are immune or idiopathic causes [4,5], whereas Type II diabetes the second category of diabetes is known as Noninsulin- Dependent Diabetes Mellitus (NIDDM) which is recognized by tissue resistance to the action of insulin combined with a relative insufficiency in insulin secretion. Insulin is produced by the β cells in these patients,

but, it is incompetent to conquer the resistance, which leads to an increment of blood glucose level. The impaired insulin action also influences fat metabolism, give rise to increased free fatty acid, triacylglycerol and diminishes high-density lipoprotein level [4,5].

The increment of blood glucose levels may affect the function of different organs such as liver, pancreas, and retina [6].

Oxidative stress is increased in DM, due to increased level production of oxygen free radicals and decreased the level of the antioxidant defense mechanisms. Higher levels of oxygen free radicals can lead to lipid peroxidation of the cellular structures, the lipid peroxidation plays an important role in the atherosclerosis development and the diabetic microvascular complications [7].

Natural compounds may be approbated to be suitable alternatives for diabetes therapy. They can decrease the risk factor of many diseases, they can consume in Large daily without any side effect as synthetic drugs [8].

Lipoic acid is an antioxidant as it has an advantageous role on the fuel metabolism and also act as an essential cofactor of mitochondrial respiratory enzymes for instance, the pyruvate dehydrogenase complex [9]. It is a natural substance antioxidant [10]. It's also known as thioctic acid, it consists of short-chain fatty acid that contain a thiol bond [11]. It is the main cofactor for energy production in the mitochondria [12].

Lipoic acid was one day theorize as a vitamin, but nowadays, it can be synthesized de novo in human cells, act as a coenzyme of multi-enzyme complexes catalyzing the decarboxylation of alpha-keto acids. Also, it is contributory the regulation of carbohydrate and lipid metabolism [13]. ALA and its reduced form, dihydrolipoate, showed a potent antioxidant to scavenge free radicals, chelated metal ions, and recycle antioxidants [12]. Also, both of them can reparation of oxidized proteins, regulation of gene transcription and inhibition of the activation of nuclear factor kappaB [14,15].

ALA has been shown to reduce the symptoms of the patient suffering from diabetes, and there are several clinical trials some efficacy and an excellent safety profile in the patient with diabetes [16,17]. So, the aim of this article review is to extend the current information and to evaluate the possible protective,

treatment and antioxidant capacity of exogenous administration of alpha-lipoic acid on the glycemic condition, beneficial for the prevention and treatment of diabetes and diabetic complications and to stimulate further research into these compounds.

Sources: External sources of ALA is not necessary for healthy individual people as their body can make its requirements. While, people that have a disease such as diabetes, liver cirrhosis, and atherosclerosis, suggests that, supplementation would be helpful as their body synthesis low dose of lipoic acid [18]. Lipoic acid is found in all foods types, but the large amount of ALA is found in the kidney, heart, liver, spinach, broccoli, and in the yeast extract [19].

The biological role of Alpha-Lipoic Acid in control Diabetes Mellitus: Alpha-Lipoic acid (ALA) has been prescribed for the treatment of DM and diabetic neuropathy, Alpha-Lipoic acid when given parenterally, can decrease blood glucose levels and improves insulin sensitivity in diabetes [14,17] Table 1.

Intravenous administration (I.V.) of Alpha-Lipoic acid (ALA) provides a metabolic benefit in patients with type II diabetes via increasing insulin-stimulated glucose disposal and insulin sensitivity. In contrast to I.V. Alpha-Lipoic acid (ALA) administration, the improvement in insulin sensitivity following oral administration of Alpha-Lipoic acid (ALA) is only minimal. This is evident despite the higher doses employed (up to 1800 mg), and the longer treatment time (30 days oral vs. 10 days I.V.) [20].

Alpha lipoic acid decreased oxidative stress, which produced by diabetes mellitus by increasing the sensitivity of insulin, thereby maintain glycemic control decrease reactive oxygen species generated by hyperglycemia and dyslipidaemia [17]. Moreover, [21] concluded that treatment with ALA with 600 mg once daily oral for four-years in mild-to-moderate diabetic distal symmetric sensorimotor polyneuropathy (DSPN) did not influence the primary composite end point but resulted in a clinically meaningful improvement and prevention of progression of neuropathic impairments and was well tolerated. Furthermore, [22] concluded that ALA has a beneficial significant effect on diabetic peripheral neuropathy symptoms.

The biological role of Alpha-Lipoic Acid of lowering lipid profile: Diabetes mellitus altered the normal metabolism of lipids in diabetic rats.

Total cholesterol and triacylglycerol (TAG) are elevated in the diabetic condition; such an elevation represented the risk factor for coronary heart disease [23].

Goldfarb and Passas (2002) reported that atherosclerosis complications and higher level in TAG which resulted due to diabetes is may be due to a reduced lipolysis of triglyceride-rich lipoproteins. In addition to the reduction in lipoprotein lipase activity which is secondary to reduced plasma insulin levels [24].

ALA can improve the dyslipidemia by decreasing the non-esterified fatty acid levels. The mechanism of action is also believed to be through the controlling activities of enzymes that involved in lipid metabolism. ALA was reported to reduce HMG-CoA reductase activities as well as increases the lipoprotein lipase and Lecithin Cholesterol Acyl Transferase (LCAT) activities [25]. Also, ALA oral administration can normalize the LDL-C levels, by controlling the hydrolysis of certain lipoprotein and their selective uptake and metabolism by different tissues.

Alpha-lipoic acid has the potential to prevent the formation of atherosclerosis and coronary heart disease which are secondary diabetic complications of severe DM [26]. The marked effects of Alpha-Lipoic acid (ALA) on risk factors for cardiovascular disease, both lipid and haemostatic are of particular importance because they indicate potential anti thrombotic and anti atherosclerotic actions that could prove beneficial in large vessel disease [27].

ALA can stimulate fatty acid oxidation by activating the AMPK in the skeletal muscles [28]. From the previous results, it could be concluded that ALA has an anti-hyperlipidemias effect on diabetes.

The biological role of Alpha-Lipoic Acid in maintaining an antioxidant defense: The number of harmful effects increases in patient with diabetes due to the accumulation of superoxide radicals and hydrogen peroxides which resulted as a result of decrease activities of antioxidant enzymes [29].

Akpinar et al. [30] found that, ALA contributes to antioxidant defense by increasing CAT activity in the stress group. The decline in catalase activity (CAT) can be attributed to ineffective scavenging of H_2O_2 resulting in increased H_2O_2 levels, which can react with O_2^- to give OH^- radical and thus increased lipid peroxidation. ALA has the ability to increase glucose

uptake in vitro [31].

Glucose, which uptake by the cells served as a substrate for the pentose phosphate shunt and oxidative phosphorylation, bringing up the cellular NADPH and nicotinamide adenine dinucleotide, therefore it enhances the activity of catalase from its inactive form [32].

Alpha lipoic acid also recycles the other antioxidants such as GSH, Alpha lipoic acid interacts with GSH and remove the free radicals in the presence of GPx [33,34]. Alpha lipoic acid increases the level of reduced glutathione not only by regenerating the existing glutathione, but also by increasing its de novo synthesis [35].

Alpha lipoic acid is characteristic by its solubility in both lipid and water solvents, So, it shows highly effective at reducing free radicals, including lipid peroxide, in cellular membrane and also it is able to gain access to the cytosol, where it effectively scavenges free radicals, capacity to regenerate endogenous antioxidants such as vitamins, E and repair oxidized proteins [11]. Tissue lipid peroxidation amelioration by ALA might also be attributed to its ability to increase glucose disposal [36]. ALA could improve the antioxidant defense mechanism by reducing free radical levels and increasing the GSH status, thereby reducing the oxidative damage that results in the patient with diabetes [37].

Alpha lipoic acid is able to supply cysteine in the body, which is an important amino acid for glutathione production. It reduces extracellular cysteine to cysteine and increases the uptake of cysteine into the cell and thus increasing glutathione production [38].

It is scientifically proven to increase cellular glutathione levels via stimulating the enzyme gamma-glutamylcysteine ligase which involved in the synthesis of glutathione, and by increasing the cellular uptake of amino acid cysteine, the limiting factor of glutathione production. Alpha lipoic acid may serve an electron donor to GPx which cause Its maximal activity [39].

The biological role of Alpha-Lipoic Acid in recycling vitamins: Hypovitaminosis is observed in diabetes. Decrease level of vitamin C may be a consequence of diabetes because cellular uptake of vitamin C is regulated by glucose and insulin [40]. Alpha lipoic acid is known to enhance ascorbic acid

formation. In addition, lipoic acid can spare ascorbic acid, this might have indirectly stimulated the ascorbic acid-dependent lipoprotein lipase activity [41].

The biological role of Alpha-Lipoic Acid in lowering MDA as oxidative stress:

Malondialdehyde is a secondary production of lipid peroxidation that used as a marker for enhanced lipid peroxidation in diabetes [42]. Malondialdehyde is chemically reactive if not remove from the soil by antioxidant mechanisms, and may cause cellular damage such as enzyme inactivation, protein and DNA damage [43].

Diabetes produce oxidative stress and cause a variety of tissue injury [44]. Hyperglycemia is the main cause of the oxidative stress in diabetes [45].

Alpha lipoic acid is able to be easily transported through cellular membranes to neutralize free radicals within aqueous and lipid regions of the cells [46].

Alpha-Lipoic Acid Nitric oxide: Diabetes revealed a significant reduction in serum NO and administration of ALA returned the serum level of NO to the control value [47]. Oxidative stress may reduce the bioavailability of NO, yielding lower NO levels, so the reduction of serum NO could be explained by the oxidative stress in diabetic patients [48].

Alpha-Lipoic Acid and kidney function test:

Lipoic acid is effective in prevention, early diabetic glomerular injury, [49,50]. It is also useful in preventing some types of tubular damage [51] as well as angiotensin II renal damage [52]. Also, ALA supplementation enhances the uptake of creatine within muscle cells [53]. This is likely to be due to the ALA's ability to enhance the uptake of glucose within muscles. ALA exerts this effect via enhancing insulin sensitivity [54,55]. Alpha lipoic acid can protect kidney tissues via inhibiting neutrophil infiltration, balancing the oxidant-anti-oxidant status, and regulating the generation of inflammatory mediators [56,57].

	Dosage	Experimental models of diabetes	Route of administration	Role	Reference
1	1200, 600, or 100 mg	Non-insulin-dependent diabetic patients	Intravenous infusion	Intravenous treatment with alpha-lipoic acid using a dose of 600 mg/day over 3 weeks showed a significant reducing symptoms of diabetic peripheral neuropathy, without causing significant adverse reactions.	Ziegler et al. (1995)
2	100 mg/kg	Male Sprague–Dawley rats	intraperitoneally	α -LA has a beneficial effect on diabetes-induced cystopathy by ameliorating oxidative stress and normalizing the NGF level in the bladder.	Jiang et al. (2008)
3	60 mg/kg/day	Wistar rats of both sexes weighing 140-150 grams	Oral	ALA was effective in restoring diabetes-induced deterioration of blood antioxidants; vitamin C and glutathione. Retinal histopathological changes observed in diabetic animals were ameliorated by administration of alpha-lipoic acid which suggests its protective role against diabetic retinopathy	El-Hossary et al. (2010)
4	300 mg twice daily for 8 weeks.	T2DM patients with age of 53 years	Capsules per os	a significant decrease in FBG and PPG levels, IR-Homeostasis Model Assessment (IR-HOMA index), and GH-Px activity in the ALA group. They concluded that the use of ALA as an antioxidant in the care of diabetic patients.	Ansar et al. (2011)
5	54 mg/kg bw daily for six weeks.	Wistar albino 220- 250 gm	Intraperitoneal, daily	Significantly decrease serum glucose, total cholesterol, triacylglycerols, LDL-C, HDL-C concentration and lipid peroxidation of liver and kidney as well as significantly increased serum vitamin C and liver catalase activity.	Hussein et al. (2012)
6	100 mg/kg per day	Eight week old male Wistar rats, weighing 200 to 250g	intraperitoneally	All changes that concomitant increased mitochondrial oxidative damage and elevated expression and activation of JNK, p38 MAPK and TGF- β can be reversed by ALA treatment, suggesting that ALA possesses therapeutic potential in the treatment of Diabetic cardiomyopathy	Li et al. (2012)

	Dosage	Experimental models of diabetes	Route of administration	Role	Reference
7	100 mg/kg 5 times a week	Adult male Wistar rats (200–250 g body weight, 8-9-weeks-old)	intraperitoneally	It may be assumed that ALA treatment protected the blood vessels walls of nerves against laminin over expression in STZ induced diabetic rats.	Aldaghi et al. (2014)
8	100 mg/kg body weight of ALA daily	Male Wistar rats 150 and 250 g	orally	administration of ALA to diabetic animals controlled the increased blood glucose concentration as well as improved the body weight	Eze et al. (2015)
9	2 mg/kg	Dogs	per os	Prevents the onset of cataract in diabetic dogs	Williams (2017)

Table 1: Dosage of ALA in some of the experimental studies

Mechanism action of alpha lipoic acid in diabetes:

Diabetes mellitus (DM) is a serious endocrine disorder, that is a main source of malady worldwide [3].

Alpha lipoic acid (ALA) is able to increase cellular uptake of glucose by recruiting glucose transporter-4 into cell membrane [58] Figure 1. Some studies suggested that treatment with racemic ALA improves insulin sensitivity [20] and glucose effectiveness by increasing pyruvate transportation into the mitochondria, increases pyruvate oxidation, and, in turn, allows glucose to enter the cytoplasm, thereby decreasing insulin resistance [59]. Post-prandial blood glucose levels drop, and glycation indicators (HbA1c) also diminish [60]. Also, [61] reported that, Lipoic acid acting as a potent antioxidant, DHLA protected rat pancreatic islet cells from destruction by reactive oxygen species.

The hypoglycemic response of alpha-lipoic acid (ALA) occurred, although liver glycogenolysis was intact. This could be explained by the fact that the contribution of glycogenolysis to glucose production is low after 12 hours' fasting. The return of blood glucose to pretreatment levels in non diabetic animals may represent the termination of the Alpha-Lipoic acid (α -LA) effect on systemic glucose production, since the half-life of Alpha-Lipoic acid (α -LA) is approximately 25 minutes [62].

The conversion of alanine, to glucose process was inhibited by alpha-Lipoic acid administration, the gluconeogenesis defect could be mapped to step between private and glyceraldehyde-3-phosphate (GA3P), in which PC and PEPCK are the two regulatory enzymes.

Konrad, (2005) mentioned the role of ALA in the translocation of glucose transporters (GLUT) from the cytoplasm to the cell surface, and results in peripheral glucose disposal. Moreover, [63] showed an attenuated in post prandial glucose in the experimental group, due to an increase in skeletal muscle glucose transport activity.

Furthermore, [64] showed that chronic administration (100 mg/kg) of the antioxidant ALA partially improved the diabetes-related deficit in glucose metabolism, and the activation of some steps in insulin signaling pathway for human T2DM.

supplementation with ALA has an effect on insulin resistance, the mechanism of action may be due to the insulin signaling pathway, such as increase in PI 3-kinase and protein kinase B [65]. The ALA has been shown to increase intrinsic activity of GLUT similarly to insulin. Activation of GLUT may be mediated by p38 mitogenactivated protein kinase [66]. Chronic ALA treatment increases both insulin stimulated glucose oxidation and glycogen synthesis, moreover, is associated with significantly lower plasma levels of insulin and free fatty acids [67]. A 3-hour exposure of primary cultured rat hepatocytes to R-ALA at therapeutically relevant concentrations increases pyruvate oxidation of the PDH complex and decreases gluconeogenesis and free fatty acids oxidation [59]. Pre-clinical studies have demonstrated that ALA improves glucose uptake and glucose oxidation, thus leading to an increase of adenosine triphosphate (ATP) synthesis.

Lipoic acid displays strong antioxidant properties and increases glucose uptake through recruitment of the glucose transporter-4 to plasma membranes, a mechanism that is shared with

insulin-stimulated glucose uptake [12]. Lipoic acid is also reported to improve neural blood flow, endoneural glucose uptake, and metabolism and nerve conduction [68]. It probably exerts its effect in diabetic patients by reducing lipid accumulation in adipose and nonadipose tissue [69], by increasing glucose uptake and by activating pyruvate dehydrogenase complex, which is known to play a

major role in the oxidation of glucose-derived pyruvate [70]. Alpha lipoic acid leads to a decrease in the severity of diabetic neuropathy by maintaining GSH levels and/or by its direct antioxidant properties [71-81]. However, lipoic acid administration improved endothelial function in subjects with metabolic syndrome.

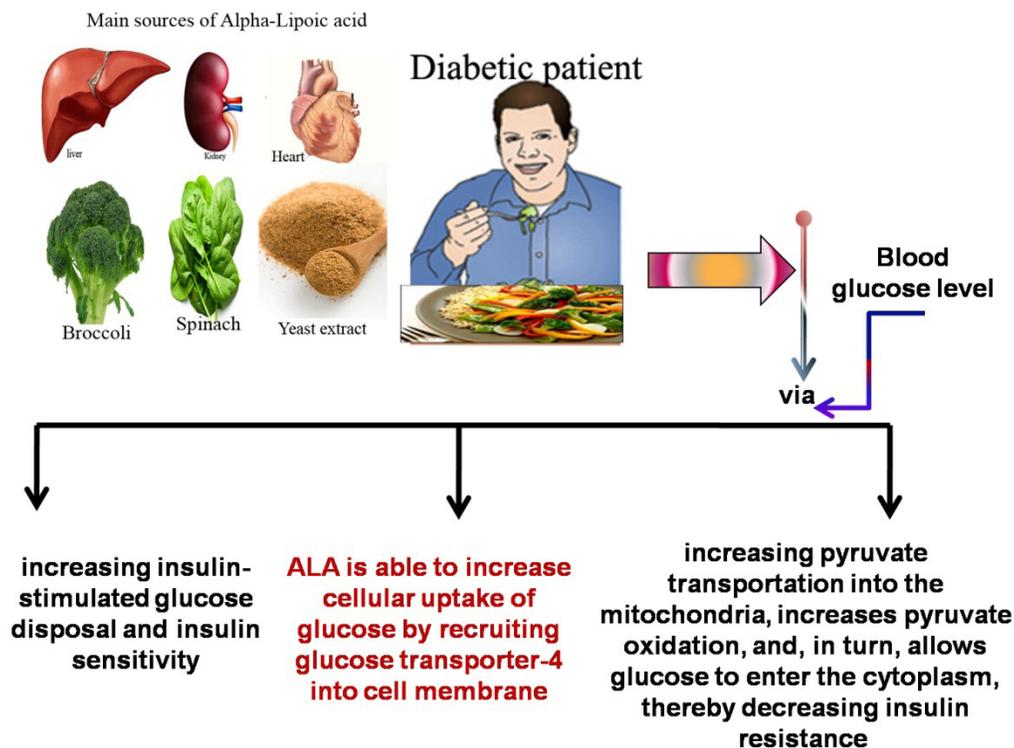


Figure 1: Mechanism action of alpha lipoic acid (ALA) in diabetes

Conclusion: This article, review has abbreviated the fundamental role of alpha lipoic acid as an antidiabetic agent. Alpha lipoic acid has the potential role in improving glucose levels, dyslipidemia and oxidative stress and may exert some protective effect on atherosclerotic vascular change in diabetes. Also, alpha lipoic acid has antioxidant properties to prevent lipid peroxidation. Additionally, alpha lipoic acid could lead to therapeutic approaches for limiting damage from the oxidation reaction in unsaturated fatty acid, as well as for complimenting, existing therapy for the treatment of complications of oxidative damage induced by diabetes.

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