

Beneficial effects of α -lipoic acid in diabetes- and drug-induced liver injury

Aleksandra Uskoković*, Svetlana Dinić, Nevena Grdović, Jelena Arambašić Jovanović, Melita Vidaković, Goran Poznanović and Mirjana Mihailović

Dept. of Molecular Biology, Institute for Biological Research Siniša Stanković, University of Belgrade, Bulevar despota Stefana 142, 11060 Belgrade, Serbia

*Corresponding author: auskokovic@ibiss.bg.ac.rs

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Abstract: This review summarizes the effects of α -lipoic acid (LA) on liver damage and complications in diabetes and drug toxicity. LA is a naturally occurring dithiol compound that plays an essential role in mitochondrial metabolism in its protein-bound form. In contrast, free LA in supplements has diverse biological actions, and its antioxidant effect is its most studied and important activity. Due to its strong antioxidant potential, LA could have a promising role in the treatment of pathologies resulting from an imbalance in redox homeostasis. This includes diabetes, which produces deleterious effects on many organs, including the liver. In diabetes specifically, LA prevents β -cell destruction, enhances glucose uptake, and its antioxidant effects may be particularly useful in slowing down the development of diabetic complications. Diabetes-related liver damage is a serious complication in which oxidative stress is the main contributor to tissue injury. Oxidative stress is regarded as one of the main pathological mechanisms underlying liver pathologies provoked by other insults, such as drug toxicity, where LA could also be a useful agent in therapeutic intervention. However, before wider application of LA in a clinical setting, experimental and clinical research needs to be extended.

Key words: α -lipoic acid; diabetic complications; liver injury; oxidative stress; nonalcoholic fatty liver disease; drug toxicity

List of abbreviations: Advanced glycation end products (AGEs); alanine aminotransferase (ALT); alpha-lipoic acid (LA); aspartate aminotransferase (AST); catalase (CAT); dihydrolipoic acid (DHLLA); free fatty acids (FFA); glutathione (GSH); glutathione oxidized (GSSG); glutathione peroxidase (GPx); heat shock proteins (HSPs); 4-hydroxy-2-nonenals (4-HNE); inhibitor of B kinase (IKK); inhibitor of NF- κ B (I κ B); insulin receptor substrate-1 (IRS-1); c-Jun NH₂-terminal kinase (JNK); Kelch-like ECH-associated protein 1 (Keap1); α -lipoic acid (LA); nitric oxide (NO); nonalcoholic fatty liver disease (NAFLD); nuclear factor erythroid 2-related factor 2 (Nrf2); nuclear factor kappa-B (NF- κ B); phosphatidylinositol 3-kinase (PI3K); reactive oxygen species (ROS); superoxide dismutase (SOD); streptozotocin (STZ)

INTRODUCTION

LA is an eight-carbon disulfide moiety-containing molecule with a single chiral center, which was first isolated and chemically identified in 1951 [1]. This naturally occurring dithiol compound is an essential cofactor for several mitochondrial enzyme complexes, including pyruvate dehydrogenase, branched chain α -keto-acid dehydrogenase and α -ketoglutarate dehydrogenase

that catalyze critical reactions related to energy production and catabolism of α -keto acids and amino acids. In humans, LA is synthesized in the liver and other tissues to a sufficient extent, meeting the requirements for its role as an enzyme cofactor in intermediary metabolism. Due to the decline of its synthesis with age [2], it is useful to supply LA exogenously from diet sources, including vegetables (spinach, broccoli, tomato) and meats (mainly viscera) or from dietary supplements [3] (Fig. 1). Naturally occurring LA in foods is covalently bound to lysine in proteins (lipoyllysine) [4]. LA is synthesized *de novo* from an 8-carbon fatty acid (octanoic acid) and cysteine (as a sulfur source) in a reaction catalyzed by lipoic acid synthase in the mitochondria, where LA functions as a cofactor for mitochondrial enzymes in its protein-bound form. Unlike endogenously synthesized protein-bound LA, supplemented LA is present in a free nonprotein-bound form. Orally supplied LA does not serve as a metabolic factor; instead it elicits biological activities, being a potent modulator of the cell's redox status, which is its most prominent activity [5]. After oral intake, LA is rapidly absorbed by the gastrointestinal tract, transported to different organs and subjected to renal excretion. LA primarily accumulates in the liver, heart and skeletal muscle, but it is also found in other tissues. Following its uptake into tissues, LA is subjected to extensive catabolism and is rapidly reduced to dihydrolipoic acid (DHLA), which is excreted from cells [5,6]. DHLA is a potent reducing agent with the capacity to reduce and regenerate intracellular antioxidants from their oxidized forms [6]. The chemical reactivity of LA/DHLA arises from the high reduction potential under physiological conditions, making this redox couple highly reactive, just below the NAD(P)H/NAD(P)⁺ pair [7]. In spite of the rapid gastrointestinal uptake of LA and appearance in the plasma which is followed by its rapid clearance, a large amount of evidence has revealed an unexpected range of cellular actions (Fig. 1). Antioxidant activity is exhibited by both the oxidized and reduced forms of LA and it includes the scavenging of reactive oxygen species (ROS) [8,9]. However, the antioxidant activity of the LA/DHLA couple has been shown in *in vitro* conditions, and it is questionable whether LA can scavenge free radicals *in vivo* since LA rapidly accumulates and is rapidly metabolized. There is growing evidence that LA can indirectly maintain the cellular antioxidant status by enhancing the synthesis of endogenous low molecular weight antioxidants, the regeneration of other antioxidants, chelation of metal ions and inhibition of redox sensitive transcription factor NF- κ B [10]. The biological activity of both LA and DHLA is an advantage when compared to other antioxidants such as glutathione, whose reduced form only has an antioxidant potential. Another advantage of LA is attributed to its water and fat solubility, unlike other antioxidants that are either lipophobic or lipophilic, which means that LA can elicit antioxidant actions in both cytosol and cell membrane compartments. In view of its potent antioxidant activity, LA has been proposed as a potential therapeutic agent in the treatment of pathologies caused by an imbalance in redox homeostasis and ensuing oxidative stress, as occurs in diabetes and its complications that affect different organs, including the liver (Fig. 1). Oxidative stress is also a contributing factor in liver pathologies provoked by exogenous insults (drug-induced toxicity), and LA could be viewed as a therapeutic agent in these conditions as well [11].

LA in diabetes

Diabetes is a metabolic disorder resulting from defective insulin synthesis due to β -cell destruction (diabetes type 1), and/or responses of target tissues to insulin or insulin resistance (diabetes type 2), which cause increased glucose concentration in the circulation or hyperglycemia, the clinical hallmark of diabetes. Different studies have provided evidence that LA stimulates glucose uptake by cardiac tissue in control and diabetic rats [12]. LA has been found to increase glucose uptake in cultured adipose and muscle cells by affecting elements of the insulin signaling pathway. LA

augments tyrosine phosphorylation and the activities of the molecular components involved in insulin signaling, including the insulin receptor (IR), insulin receptor substrate (IRS)-1, phosphatidylinositol 3-kinase (PI3K), Akt1 and p38 [13]. Specifically, stress-activated kinases such as c-Jun NH2-terminal kinase (JNK) and the inhibitor of B kinase-(IKK) interfere with normal insulin signaling by phosphorylation of the serine in IRS-1, reducing its interaction with the downstream effector PI3K. Thereby these kinases play an important role in insulin resistance progression. It was revealed that LA inhibited the JNK pathway and IRS-1 serine phosphorylation, and improved insulin sensitivity [14]. The underlying mechanism by which LA improves insulin signaling could be at least in part attributed to LA-mediated induction of heat shock proteins (HSPs) that have the potential to inhibit JNK and IKK [15]. Clinical studies showed that LA increased insulin-stimulated whole-body glucose disposal in diabetic patients [16].

LA has potential applications in various aspects of diabetes pathophysiology, ranging from effects on insulin-producing pancreatic β -cells to long-term diabetic complications (Fig. 2). It is assumed that the effects of LA on β -cells are dose-dependent, meaning that at higher concentrations LA exerts detrimental effect, whereas at lower and clinically approved concentrations it produces beneficial and cytoprotective effects on β -cells in diabetes [10]. Another potential beneficial effect of LA in diabetes is based on its ability to inhibit protein glycation, which is assumed to be an important factor in the development of diabetic complications. This effect of LA is not based on its antioxidant potential but rather on the non-covalent hydrophobic interaction of LA with target proteins, which blocks the protein glycation site and prevents its glycation [10].

A direct link between oxidative stress in diabetes and pathogenic events that lead to diabetic complications has been established. Hyperglycemia promotes increased production of ROS via different pathways (nonenzymatic, enzymatic and mitochondrial), which together with impaired antioxidant defenses results in increased oxidative stress. The persisting imbalance in redox homeostasis in diabetes activates the expression of inflammation related genes via stress signaling pathways, stimulating the establishment of an inflammatory state. The oxidative stress-activated proinflammatory pathways are a complex pathogenic mechanism that promotes a variety of diabetic complications in different tissues and organs, including the liver. According to clinical evidence, the strong antioxidant effects of LA have been shown to be particularly useful in treating diabetic neuropathy [4]. A daily oral dose of 600 mg provides an optimum risk-to-benefit concentration in human diabetics [5]. Hence, the antioxidant potential of LA self-recommends the use of this compound in therapeutic approaches aimed at attenuating the development of diabetes associated complications.

LA and diabetes-related liver pathologies

Diabetes is one of the most common causes of liver disease, which is an important contributor to increased mortality in diabetic patients [17]. Fatty liver, insulin resistance and obesity are endogenous factors that provoke liver dysfunction in diabetes [18]. Fatty liver belongs to nonalcoholic fatty liver disease (NAFLD), which represents a spectrum of hepatic disorders, starting from steatosis characterized by excess fat accumulation within hepatocytes that can progress to steatohepatitis when accompanied by inflammation (hepatic fibrosis), and further to cirrhosis and ultimately liver failure. The prevalence of NAFLD in obese patients with diabetes type 2 is greater than 70%. Decreased insulin-dependent suppression of lipolysis in adipose tissue results in elevated levels of circulating free fatty acids (FFA), which accumulate in the liver where synthesis of triglycerides occurs. Impaired hepatic fatty acid oxidation and very low-density lipoprotein secretion, as well as increased glucose concentrations in diabetes provide additional

contributing factors to triglyceride synthesis that leads to hepatic fat accumulation. According to literature data, the use of supplements comprised of different antioxidant compounds including LA has been approved for treatment of patients suffering from fatty liver and nonalcoholic steatohepatitis in Mexico [19].

Most of the pathological changes in liver morphology and function observed in diabetes are the result of oxidative stress-mediated injury (Fig. 3). The prooxidant environment established by free radical formation in diabetes contributes to oxidative stress development. The sources of free radicals in diabetes originate from nonenzymatic pathways (the production of hydroxyl radicals (OH•) via glucose autooxidation, formation of advanced glycation end products (AGE), over stimulation of the polyol pathway), enzymatic pathways (involving nitric oxide synthase, NAD(P)H oxidase and xanthine oxidase), and mitochondrial pathways with the mitochondrial respiratory chain as the main nonenzymatic source of ROS [10]. It is assumed that mitochondrial production of the superoxide anion radical ($O_2^{\bullet-}$) provoked by hyperglycemia is the main trigger of events leading to oxidative stress in diabetes [20,21].

The most important enzymatic antioxidants that cope with free radicals involve superoxide dismutase (SOD) that catalyzes the dismutation of the superoxide radical to form hydrogen peroxide (H_2O_2) and oxygen, catalase (CAT) that converts H_2O_2 to water and oxygen, and glutathione peroxidase (GPx) that reduces H_2O_2 using reduced glutathione (GSH) to form oxidized glutathione (GSSG) and water. Of the nonenzymatic cellular antioxidants, the low molecular weight GSH molecule is very important. It plays a crucial role in maintaining protein thiols in a reduced form [22,23]. The impairment of the antioxidant defense system has been demonstrated in diabetes. It is an additional risk factor that contributes to oxidative stress-related liver injury (Fig. 3). Therefore, aside from the search for protective antioxidant effects that interfere with ROS overproduction, attempts at improving the intrinsic antioxidant defense system that preserves redox homeostasis is also an important approach to preventing oxidative stress-related pathologies. LA may indirectly affect the cellular antioxidant response through increased uptake or synthesis of endogenous low molecular weight antioxidants. LA increases intracellular GSH through improved cystine uptake from the plasma, followed by its reduction by DHLA to cysteine, which is the substrate for GSH synthesis [5]. It was shown in different cultured cells that DHLA increases GSH synthesis by reducing cystine to cysteine [24]. In addition, LA induces the *de novo* synthesis of GSH at the transcriptional level by directly modulating cellular signaling pathways [25]. It was shown that the administration of LA promoted the restoration of the GSH:GSSG ratio increased the protein thiol content in the liver of streptozotocin (STZ)-induced diabetic rats. The antioxidant and hepatoprotective effects of LA in STZ-induced diabetic rats also include improvement of the activities of the antioxidant enzymes SOD and CAT [26,27]. LA affects CAT and CuZnSOD expression in the liver at the transcriptional level. The post-translational mechanism including decreased O-GlcNAcylation of CAT and SOD, upstream kinases and transcriptional factors involved in the regulation of enzyme expression is also involved in the LA-mediated upregulation of antioxidant enzyme expression [26]. This antioxidant effect was followed by hypoglycemic activity of LA, resulting in a lower level of DNA damage and improved activities of the indicators of hepatocellular injury, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), suggesting that LA exerted hepatoprotective effects in diabetes [26].

An important role in the transcriptional regulation of the antioxidant defense system is ascribed to transcription factor-nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 is located in the cytoplasm where it associates with cytoplasmic repressor Kelch-like ECH-associated protein 1 (Keap1), which maintains Nrf2 in its inactive form. Different activators and inducers of Nrf2 are

capable of releasing Nrf2 into the nucleus, where it transactivates detoxifying and antioxidant enzymes. LA is one of the inducers of Nrf2-mediated antioxidant gene expression and in as such it can increase GSH synthesis [28]. It has been reported that Nrf2 can play a significant role in the attenuation of oxidative stress through the suppression of proinflammatory signaling pathways [29]. NF- κ B is a central mediator of inflammatory processes whose activation in hyperglycemia contributes to diabetes pathology and its associated complications [30]. NF- κ B is located in the cytoplasm in an inactive form in a complex with a family of NF- κ B inhibitor (I κ B) proteins. Upon stimulation, IKK α and β are activated, which results in the phosphorylation of I κ B and its proteasomal degradation that release NF- κ B, allowing it to translocate into the nucleus where it induces gene expression [31]. The increased activation of NF- κ B in hyperglycemia and resulting transactivation of key target genes involved in inflammatory processes result in systemic and local deleterious effects that contribute to the development and progression of diabetic complications. NF- κ B and its target genes, such as proinflammatory cytokines, TNF, IL-1 and IL-6, are crucial factors in the development of insulin resistance, which is an important component in the etiology of type 2 diabetes. Activation of NF- κ B and chronic inflammation in the liver mimics the insulin resistance induced by obesity. Consequently, inhibition of NF- κ B activity in the liver decreases the expression of NF- κ B target genes that attenuates type 2 diabetes. Inhibition of cytokine-induced NF- κ B activation was shown to protect pancreatic β -cells from cytokine-induced apoptosis in an experimental model of STZ-induced diabetes [30]. Thereby, inhibition of NF- κ B activation could potentially be an effective strategy and important aspect in diabetes treatment through β -cell protection and amelioration of the diabetes phenotype. It has been shown that LA is capable of inhibiting IKK α and β , and consequently I κ B degradation, which results in the inhibition of NF- κ B-mediated gene expression, suggesting that LA prevents NF- κ B activation in a mechanism that does not involve its antioxidant potential [32].

In addition to the disturbance of the antioxidant system, impaired expression of HSPs also appears to play an important role in the pathophysiology of diabetes. It has been reported that formation of the LA disulfide can play a significant role in the activation of the heat-shock response in diabetes [9,33,34]. Under diabetic conditions, LA application increased the expression of HSP90 and HSP72 that have an important place in the cell's machinery for protein folding and stabilization [35]. HSP60 functions as a mitochondrial chaperone responsible for the transport and refolding of proteins from the cytoplasm into the mitochondrial matrix. Under oxidative stress, among the reactive lipid peroxidation products, 4-hydroxy-2-nonenals (4-HNE) is a biomarker that modulates a number of signaling processes through its ability to form covalent adducts in proteins, nucleic acids and membrane lipids. Increased oxidative stress in diabetes impairs hepatic HSP and induces 4-HNE production. It was observed that LA increased HSP60 and decreased 4-HNE in the liver [33].

Protective effects of LA in drug-induced liver injuries

Drug-induced liver injury is the most common cause of acute liver failure in the USA and western Europe [36]. Drug-induced liver injuries are dose-dependent, as demonstrated by acetaminophen-induced liver toxicity, which represents the most common cause of acute liver failure in the USA. More than 900 drugs (certain medicinal agents, chemical agents used in laboratories and industries, natural compounds and herbal preparations) have been implicated in liver injury [37]. The most common reason for the subsequent removal of a clinically accepted drug is drug-induced hepatic injury. The mechanism of drug-induced liver injury includes apoptotic and necrotic hepatocellular cell death, the production of ROS, mitochondria damage, specific immune reactions and altered signaling pathways [38,39] (Fig. 4). Drugs or their reactive metabolites are detoxified through

oxidation and reduction by polymorphic cytochrome P450 (CYP450) family enzymes. Covalent binding of drugs or their reactive metabolites to the P450 enzyme acts as trigger of the immune response. Hepatotoxic reactive metabolites directly and through secondary toxic damage bind to cell structures and induce GSH depletion. Reactive metabolites can inhibit the bile salt efflux pump that is responsible for the exclusion of endobiotic and xenobiotic substrates from hepatocytes into the bile [40,41]. Depletion of GSH induces the production of mitochondrial ROS and consequently mitochondrial dysfunction. On the other hand, increased production of ROS triggers protective antiinflammatory and antioxidant pathways, including upregulation of Nrf2 signaling, which increases GSH synthesis and ROS detoxification [42,43].

Chloroquine is commonly used as an antimalarial and antirheumatoid agent. Compared to silymarin, a reference hepatoprotective drug, orally administered LA against chloroquine-induced hepatotoxicity in Wistar rats showed significantly improved levels of plasma antioxidants, GSH, vitamin C and vitamin E, as well as decreased serum levels of AST, ALT, alkaline phosphatase, bilirubin, lipids and plasma thiobarbituric acid-reactive substances and hydroperoxides [44]. Bromobenzene, which is primarily used as an additive to motor oil, is formed during pesticide manufacturing, chlorination of drinking water and in the rubber industry, and is resistant to biodegradation after outflow to the environment. It has been documented that bromobenzene hepatotoxicity can lead to hepatic necrosis. Oral administration of LA in bromobenzene-induced toxicity to albino rats significantly increased the hepatic GSH content, normalized hepatic lipid peroxidation and nitric oxide production, and preserved hepatocyte architecture [45]. Methotrexate is an effective cytotoxic drug and has been used in treatment of malignancies and inflammatory diseases, but long-term methotrexate use can cause hepatic steatosis, fibrosis and cirrhosis. LA treatment of Wistar albino rats reversed liver GSH levels, malondialdehyde and (Na⁺/K⁺)-ATPase activities as well as the histopathological alterations induced by methotrexate [46]. The beneficial effects of LA against CCl₄ and thioacetamide-induced hepatotoxicity have also been documented [47-49].

A beneficial outcome of LA supplementation was also observed in other types of liver injury, such as increased alcohol intake or intake of environmental contaminants. Additional causes of acute liver failure are neoplastic infiltration, heatstroke, mushroom ingestion, mycotoxins, metabolic diseases such as Wilson's disease and viral infections (hepatitis A, B and E) [50]. Alcoholic liver disease is related to changes in the liver, including steatosis, fibrosis and cirrhosis with increased risk for the development of hepatocellular carcinoma [51]. Through cellular reduction to DHLA and the ability to normalize the NADH/NAD⁺ ratio, and increase the concentration of GSH and (Na⁺/K⁺)-ATPase activity, LA provides a valuable effect in alcohol intoxication. Aflatoxin B1 is the most biologically active form of aflatoxins, very dangerous mycotoxins produced mainly by *Aspergillus flavus* and *Aspergillus parasiticus* with high toxicity in animals and humans. Administration of LA prevented liver damage in broilers induced by a chronic low dose of aflatoxin B1, improved liver histopathological parameters and liver glutamic oxaloacetic transaminase and glutamic pyruvic transaminase activities [52]. Administration of lipopolysaccharide from Gram-negative pathogens contributes to the development of liver dysfunction and septic hepatic failure. Administration of LA to Wistar rats subjected to sepsis prevented the increase in pro- and antiinflammatory cytokines (IL-1 β , IL-6, TNF- α , IL-10). In addition, LA treatment decreased liver antioxidant enzymes (GPx, SOD, xanthine dehydrogenase and xanthine oxidase), lipid peroxidation and total serum NO levels [53,54].

CONCLUSION

Considering the strong antioxidant potential of LA, its use as a therapeutic agent in treatment of diseases whose development and progression are closely linked with disturbed redox homeostasis is promising. The main hepatoprotective effects of LA cover the activities that result in decreased oxidative stress, inflammation, DNA damage and fibrotic processes. Despite efforts made in unraveling the importance of antioxidant action, including the effects of LA against oxidative-stress-related diseases such as diabetes and liver diseases, as well as promising results obtained in experimental studies and clinical trials, antioxidative therapy still has to be developed. Many antioxidants are highly effective in animal models of hepatic disorders, but in humans their beneficial influence in treating the same liver diseases is not effective. Therefore, detailed translational research is required for the establishment of antioxidant therapy in clinical practice for treating hepatic disorders triggered in diabetes as well as by drug inducers.

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Figure Legends

Fig. 1. LA structure and effects. LA and its reduced form DHLA, with the most prominent functions related to insulin sensitivity, diabetic neuropathy, oxidative stress (LA increases intracellular GSH and regenerates ascorbic acid, vitamin E and coenzyme Q10), inflammation and mitochondrial metabolism.

Fig. 2. Roles of LA in diabetes. LA protects pancreatic β -cells, improves glucose uptake, attenuates insulin resistance and ameliorates diabetic complication.

Fig. 3. Antioxidant effects of LA against oxidative stress-related liver injury in diabetes. LA affects redox homeostasis towards decreased ROS production and increased antioxidant system potential.

Fig. 4. Drug-induced liver injury. Drug or reactive drug metabolite induce the expression of cytochrome P450 enzymes which generate ROS and in turn covalently bind to cellular macromolecules, cause GSH depletion, impair mitochondrial function, inhibit biliary efflux and the innate immune response. The result is hepatocyte cell death by apoptotic or necrotic pathways.

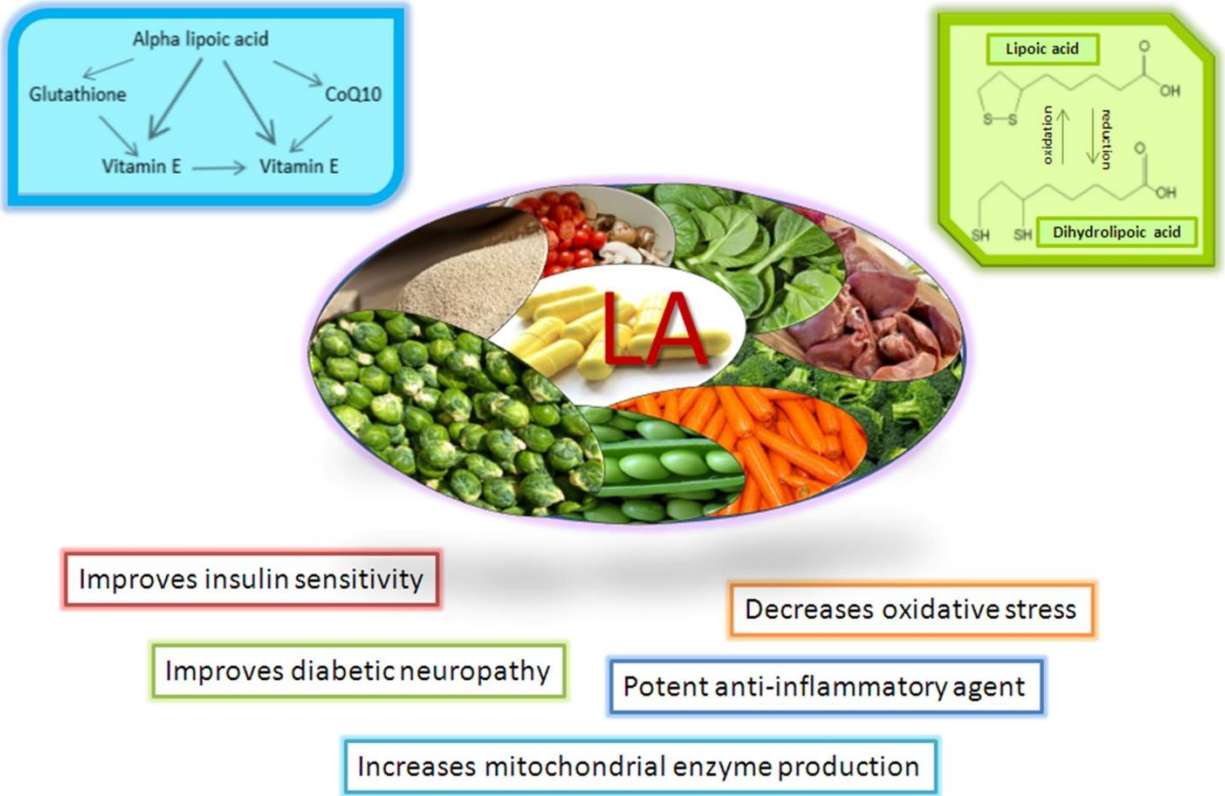


Fig. 1.

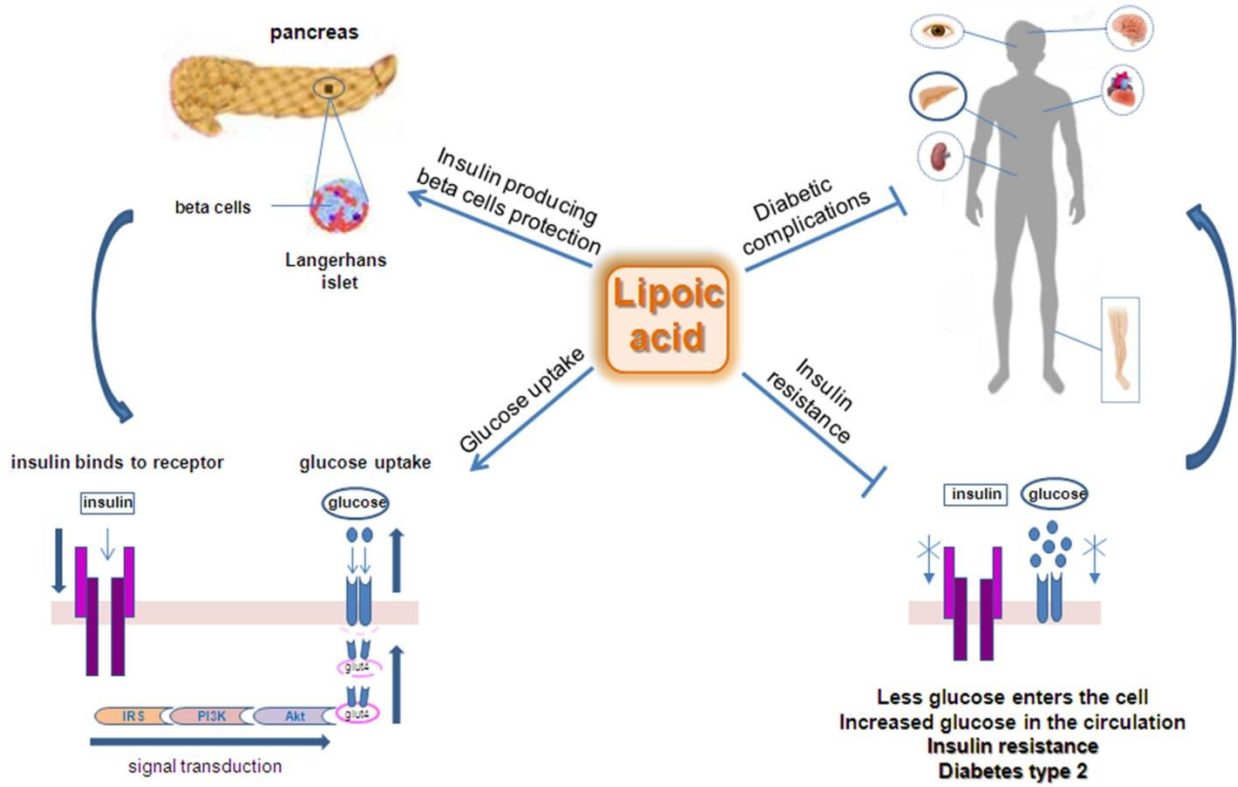


Fig. 2.

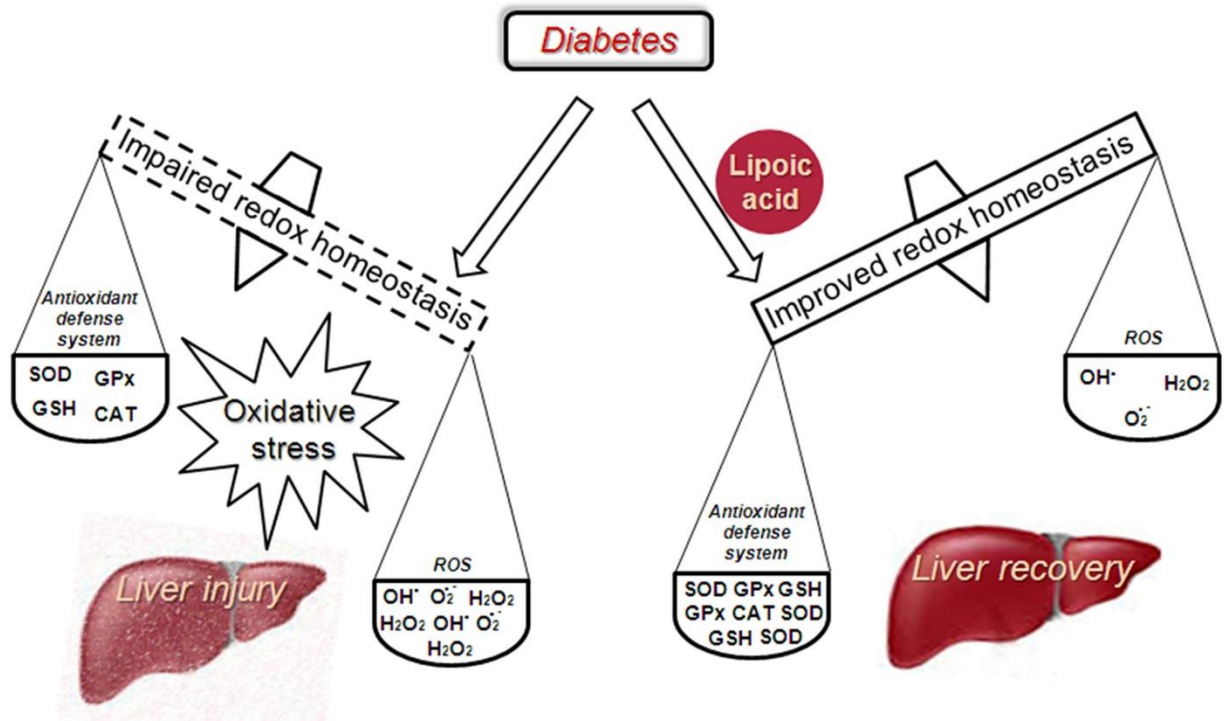


Fig. 3.

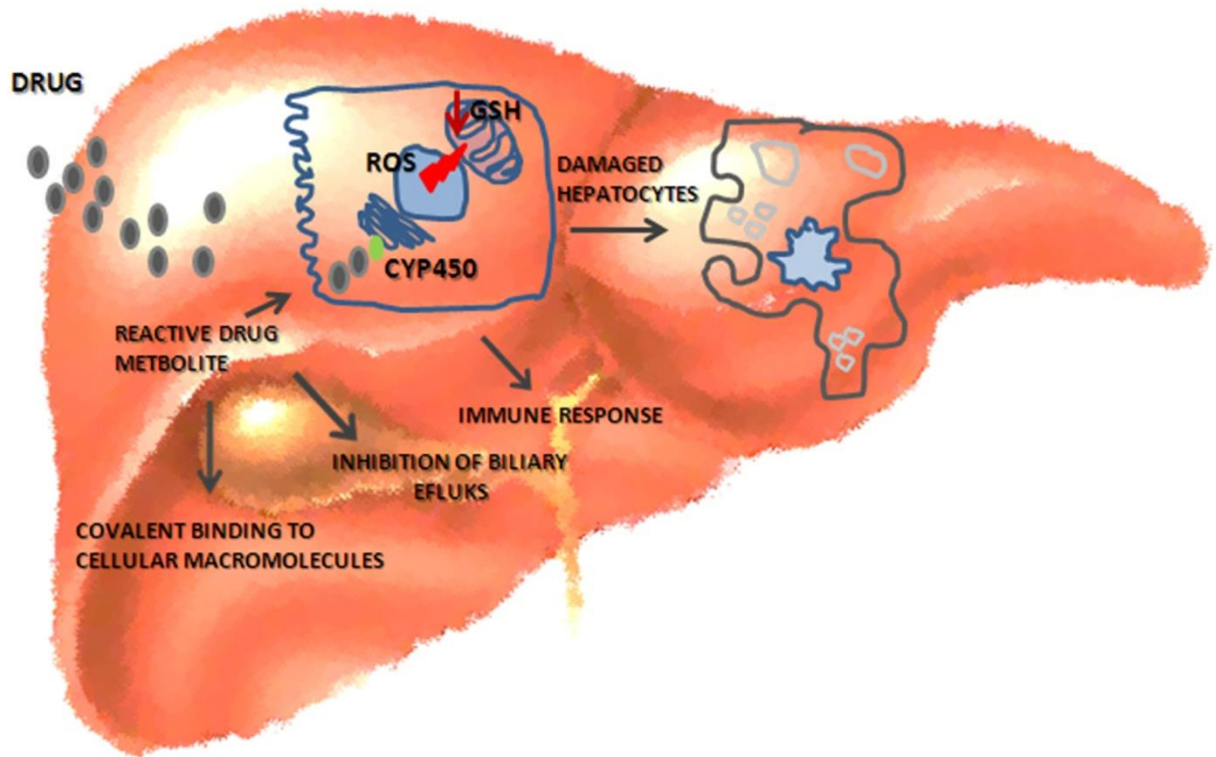


Fig. 4.