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Current Topics in Medicinal Chemistry, 2015, *15*, 000-000

Lipoic Acid: Its Antioxidant and Anti-Inflammatory Role and Clinical Applications

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Abstract: Lipoic acid (LA) is an antioxidant able to produce its effects in aqueous or lipophilic environments. Lipoate is the conjugate base of lipoic acid, and the most prevalent form of LA under physiological conditions. It presents a highly negative reduction potential, increases the expression of antioxidant enzymes and participates in the recycling of vitamins C and E. Due to these properties, LA is called the "universal antioxidant". LA is also involved with anti-inflammatory action, independently of its antioxidant activity. This review was carried out, aiming to identify, analyze, and rationalize the various clinical, physiopathological and/or physiological situations in which LA, through oral supplementation, was tested on human and animal (rats and mice) models. LA was mainly tested in cardiovascular diseases (CVD), obesity, pain, inflammatory diseases and aging. LA uses in CVD and obesity, in humans, are controversial. On the other hand, beneficial effects on inflammation and pain were observed. LA supplementation in animal models may prolong life, has neuroprotective effects and presents positive effects against cancer. Differences observed in human and animal models can be due, in part, to different treatments (LA combined with other antioxidants, different doses) and to the variety of biomarkers investigated in animal experiments. These results suggest the need for further clinical trials to guide health professionals regarding the safety of prescription of this supplement.

Keywords: Inflammation, lipoic acid, oral supplementation, oxidative stress.

1. INTRODUCTION

Several studies aim to understand the physiopathological mechanisms of diseases, trying to identify potential agents, natural or synthetic, which effectively act in the prevention and/or treatment of them.

Among these substances, the 1,2-dithiolane-3-pentanoic acid, also known as α-lipoic acid (LA), lipoic acid or thioctic acid, has a redox active disulfide group. The carbon atom at C6 is chiral and the molecule exists as two enantiomers (*R*)-(+)-lipoic acid (RLA, the biologically active enantiomer) and (*S*)-(-)-lipoic acid (SLA) and as a racemic mixture (*R*/*S*)-lipoic acid (R/S-LA). The reduced form of LA, known as dihydrolipoic acid (DHLA), a dithiol compound, interacts with reactive oxygen and reactive nitrogen species (RONS) [1], and both forms act as antioxidants [2,3]. It is important to note that exogenous LA is rapidly internalized by cells and reduced to DHLA [4].

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Due to its antioxidant and anti-inflammatory characteristics both *in vitro* and *in vivo*, oral supplementation of LA has been tested in diabetes treatment and its cardiometabolic complications [5], cancer [6], neurological disorders such as epilepsy [7], and others.

LA is able to produce its effects in aqueous or lipophilic [1,2,8] environments. Despite its insolubility in water (2.24 x 10^{-1} g/L), its conjugate base, lipoate, is more soluble and the most prevalent form of LA under physiological conditions. It has a highly negative redox potential of -0.32 V (vs. Normal Hydrogen Electrode) [9] and for all these reasons, the redox couple LA/DHLA is called an "universal antioxidant" [10,11]. In addition, LA is capable of reducing the oxidized form of nicotinamide adenine dinucleotide phosphate ($NADP^+$), to restore the reduced/oxidized glutathione (GSH/GSSG) ratio, in favor of GSH, to increase the expression of antioxidant enzymes such as glutathione reductase [12], as well as to participate in the recycling of vitamins C and E [4] (Fig. **1**).

Inflammation, a clinical condition closely related to redox imbalance, found in several diseases such as cardiovascular diseases (CVD) [13-16], cancer [17-19], and others [20-24], also presents its clinical evolution reduced/suppressed in the presence of LA. Among the proposed mechanisms to justify

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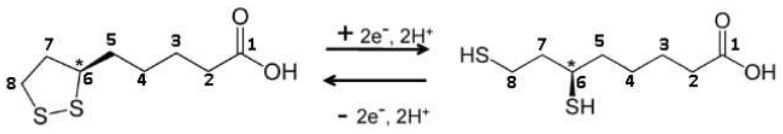

Lipoic acid (LA) Dihydrolipoic acid (DHLA)

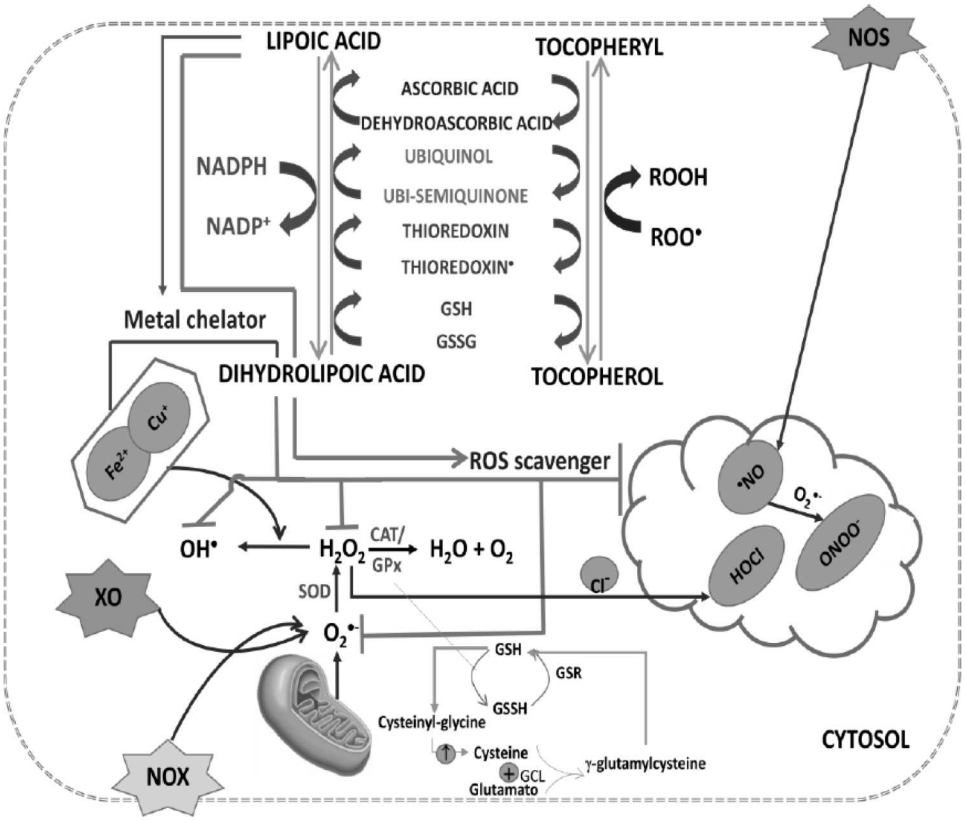

Fig. (1). The effects of LA on reactive oxygen and nitrogen species (RONS) pathways: LA ands DHLA behaves as a RONS scavenger (·NO, $O_2^{\bullet-}$, HOCl, H_2O_2, $ONOO^-$, OH·), metal chelator (Fe^{2+}, Cu^+) and regeneration agent (tocopheryl, ascorbic acid, ubi-semiquinone, thioredoxin and reduced glutathione).

Legend: + = increased the expression; ↑ = increased cellular uptake; CAT (catalase); GCL (Glutamate cysteine ligase); GPx (Glutathione peroxidase); GR (Glutathione reductase); GSH (Glutathione reduced); GSSH (Glutathione oxidized); GSR (Glutathione reductase); H_2O (water); HOCl (hipoclorous acid); $NADP^+$ (Nicotinamide adenine dinucleotide phosphate); NADPH (Nicotinamide adenine dinucleotide phosphate reduced); ·NO (oxide nitric); NOS (oxide nitric synthase); NOX (Nicotinamide adenine dinucleotide phosphate oxidase); $O_2^{\bullet-}$ (superoxide anion radical); O_2 (oxygen); $ONOO^-$ = peroxynitrite; OH· (hidroxyl radical); SOD (superoxide dismutase); XO (xanthine oxidase).

Scavenger Production

this action, there is suppression of genes involved in inflammatory activity such as Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells (NF-κB) [25-28], increase of the expression of genes for anti-inflammatory proteins, such as Nuclear erythroid 2-related factor (Nrf2) [29], as well as reduction in the concentration of several pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and Interleukin 6 (IL-6) [30,31], independent on its antioxidant activity [32] (Fig. **2**). However, due to its accumulation in tissues after oral ingestion, as well as its pro-oxidant activity [9,33,34] the efficacy of oral supplementation of LA has been questioned [35,36].

Several reviews about LA have been published in several databases, in an attempt to elucidate its biochemical [37,38], clinical [4,39,40], pharmacological and/or nutritional [2,41,42] and antioxidant [1], [43-44] actions. A extensive survey, in the context of the use of LA in various pathologies was published by Shay in 2009, where the authors discuss the use of LA in diabetic polyneuropathy, in the vascular system, in hypertension and in the inflammatory process [2].

Thus, the main objective of this review is to update the last review, attempting to rationalize the various clinical, physiopathological and/or physiological situations in which LA, through oral supplementation, was tested on human and animal (rats and mice) models, aiming to critically define the plausible health benefits of LA oral supplementation.

2. METHODS

A review using the databases of PubMed, ScienceDirect and Web of Science was conducted, using a combination of the following terms: lipoic acid/thioctic acid, oral supplementation, oxidative stress (OS) and inflammation. References cited in publications that were found were also used.

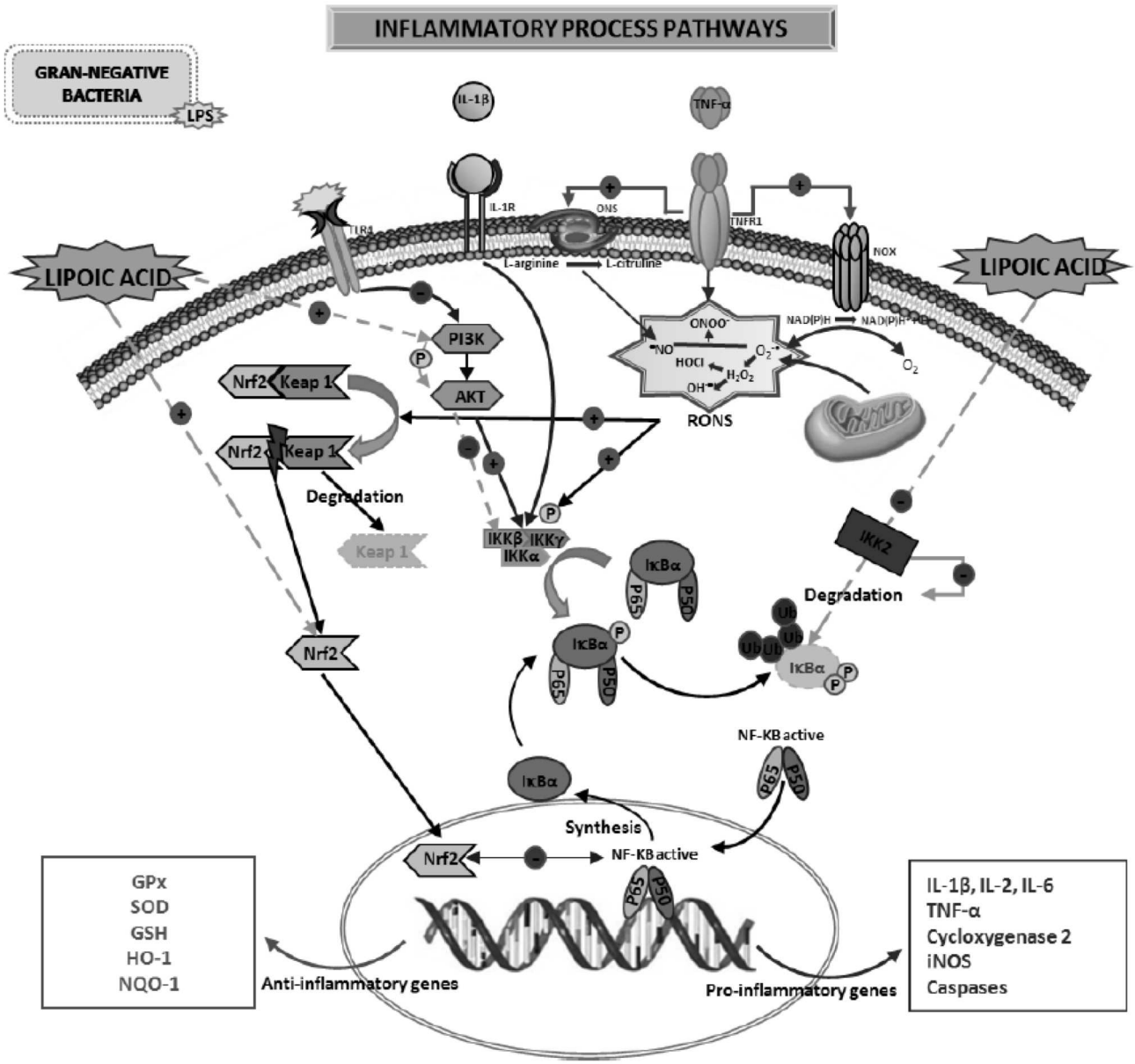

Fig. (2). Some anti-inflammatory effects of LA: Cytokines such as TNF-α (Tumor Necrosis Factor α) and IL-1β (Interleukine 1 beta) are produced in the inflammatory processes and are recognized by their receptors present on cell membranes. TNF-α receptor 1 (TNFR1) activation produces 3 actions: 1) NADP(H) (nicotinamide adenine dinucleotide phosphate) complex activation which converts NAD(P) (Nicotinamide Adenine Dinucleotide) to NADP(H) (nicotinamide adenine dinucleotide reduced) with O_2 and $O_2^{\cdot-}$ production. 2) Nitric Oxide Synthase (NOS) activation that converts L-arginine to L-citruline with Nitric Oxide (·NO) generation; and 3) own ROS (reactive oxygen species) production. These RONS (reactive oxygen and nitrogen species) generated activate cellular pathways which promote IKK complex (IKKβ, IKKα and IKKγ) phosphorylation that leads to the phosphorylation of the NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) inactive form (IκBα-P65-P50). This inactive form undergoes another series of phosphorylations plus ubiquinations which have as a consequence IkBa subunit degradation and NF-kB active form release. After its activation, NF-kB enters in the nucleus and increases pro-inflammatory and pro-apoptotic genes expression. Parallel to these reactions, the RONS stimulate the breakdown of the Keap1 (Kelch ECH associating protein 1) and Nrf2 (Nuclear erythroid 2-related factor) crossover. The free Nrf2 enters the nucleus and leads to the anti-inflammatory and antioxydant enzimes genes' expression. Intracellular concentrations of NF-kB inhibit Nrf2 (Nuclear erythroid 2-related factor) action and vice versa. Another pro-inflammatory mechanism is mediated by LPS (lipopolysaccharides), the major component of the utter membrane of Gram-negative bacteria. The inhibition of phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway activates NF-kB, Among the different anti-inflammatory mechanisms 1) LA inhibits IKK2 subunit (IκB kinase-2) degradation and inflammatory gene expression; 2) LA increases Nrf2 levels but does not affect nuclear levels of Keap 1; and 3) LA causes Akt phosphorylation by activating the PI3K pathway. This phosphorylation causes inhibition of NF-kB. Adapted from Shay [138], Ying [98] and Zang [139].

Legend: GPx = glutathione peroxidase; HOCl (hipoclorous acid); IL = interleukin; iNOS = inducible nitric oxide synthase; SOD = superoxide dismutase; HO-1 = Heme oxygenase 1; NQO-1 = quinone oxidoreductase 1; $O_2^{\bullet-}$ (superoxide anion radical); O_2 (oxygen); $ONOO^-$ = peroxynitrite; $OH^{\bullet}$ (hidroxyl radical).

Articles published from 2009 (publication year of the review done by Shay [2]) to November 2014 that used animal models (rats or mice), as well as researches using humans (others than case related studies) were included. Articles in which LA was used alone or combined with other substances through oral supplementation/administration were included. To minimize losses, the search was conducted by two researchers, independently.

Initially, the papers titles were read, with exclusion of duplicate articles. Thereafter, the abstracts were read, and subsequently, the articles that did not fit the inclusion criteria or did not make the route of administration of LA clear, were excluded.

Finally, the articles were grouped into the following categories: obesity and cardiometabolic diseases (obesity, hypertension, atherosclerosis, dyslipidemia, heart diseases, diabetes mellitus, non-alcoholic liver disease and metabolic syndrome), aging, neurological disorders, cancer, pain, inflammatory diseases and others.

3. RESULTS

One hundred-twenty two articles were found, with 50 (41.0%) articles related to tests conducted in humans (Table **1**) and 72 (59%) in animals (Table **2**). LA was used in several clinical conditions and all them have OS and/or inflammatory activity involved in their etiopathogenesis.

4. DISCUSSION

4.1. LA, Historical Aspects

Lipoic acid (LA) was first isolated from bovine liver in 1951 by Reed [163]. In this publication, the authors identified the acetate-replacing factor, a substance that restored growth on pyruvate dehydrogenase complex (PDC) in a mutant strain of *Streptococcus faecalis* and called it, lipoic acid due to its high solubility in organic solvents. Furthermore, LA is involved in the production of acetate, a precursor of fatty acids. Since then, several papers have analyzed the chemical and physiological aspects of this acid [163-165].

In 1954, Mardones [166] clinically tested synthetic LA on voluntary alcohol intake in rats, since, according to the authors, the increase in alcoholic consumption could be caused by a disturbance in the metabolism of carbohydrates due to the reduced levels of the so-called "N factor." In conclusion, the study demonstrated that deficiency of LA, along with other substances, unknown until then, would be responsible for the increase in alcohol consumption of these animals, possibly due to its catalytic role together with pyruvate dehydrogenase (PDC) [167].

Although its action on redox reactions was firstly described in 1955 [113], its anti-inflammatory role only became evident in 1977, with studies evaluating its action on the biosynthesis of prostaglandins [168,169].

In 2009, Shay [2] selected various clinical trials that tested the therapeutic potential of oral and intravenous supplementation of LA. About security of LA dosage, the authors concluded that moderate doses (up to 1800 mg/day) are considered safe. However high or chronic doses or when LA is administered, intraperitoneally, at a dosage of 5 to 10 g/day, it can raise blood levels of hydroperoxides. The authors concluded that the biological effects of LA are diverse, such as cell signaling inducer, insulin-mimetic, hypotrigliceridemiant, vasorelaxant/anti-hypertensive agent, chelator of various metals and neurocognitive adjuvant.

4.2. LA Supplementation in Obesity and Cardiometabolic Disorders is More Effective in Animal Models

Tables **1** and **2** show that most of the studies (n = 36, 29.8 %) evaluated the use of LA in obesity and cardiometabolic diseases. Important differences can be observed among the results obtained from human and animal studies. In animal models, many positive outcomes were identified, such as reduced body/fat weight [98,105,170,171], improved redox balance [109,111,172,173], glycemic [102,106,112,170,174] and lipid [98,102,103,108,171] control, reduction of intra-hepatic fat [28,114,116], as well as reduction of apoptosis [110] and inflammatory process [107,172], and improvement in diabetes complications [107-109], with the only exception in the increased of cornea protein carbonylation [149] and generation of superoxide radical by mitochondria [116].

In human studies, upon LA supplementation, a small number of positive effects were identified, such as decrease in body weight [36,45,48], increased visual acuity [53] and protection against glomerular podocyte injury [51], in diabetic subjects. However, they have not identified any action on glucose [49], [50,52] or lipid profile [48]. In fact, adverse effects were observed, like increased low-density lipoproteins (LDL) oxidation [47] and carboxymethyl lysine levels [50], nullification of the positive effects of exercise on blood pressure [47] and worsening of diabetic peripheral neuropathy [57]. An exception is observed in the study of Porasuphatana [55], with type 2 diabetes patients who received LA (300, 600, 900 or 1200 mg/day), for a period of 6 months. The authors found a significant decrease in postprandial glucose levels, glycated hemoglobin and lipid peroxidation. It is important to emphasize that drug treatment for the control of diabetes remained throughout the period of LA supplementation [55]. Witman [46] also observed a positive effect of LA. The authors identified an increase of endothelium-dependent vascular function in subjects with > 14 years pos-heart transplant who received an antioxidant complex, containing LA. It is useful to emphasize that the role of LA, itself, was not studied, since a mixture of antioxidants was used (vitamins C and E, together with LA).

It is worthy to mention that although only 4 studies on diabetic neuropathy in humans have been found, several meta-analyses confirm the therapeutic effect of LA supplementation for 3-5 weeks, in improving pain caused by this disease [175-177].

The effect of LA on the decrease of body weight is still not fully understood [36], however it could be partly explained by the suppression of protein kinase AMPK (5'Adenosine Monophosphate-activated Protein Kinase, AMPK), whose hypothalamic action is critical for regulation, not only for food intake but also for energy expenditure elevation [178].

Table 1. Oral supplementation action of lipoic acid (LA) alone or in association with other antioxidants in humans: articles published from 2009-2014.

Author	Clinical Situation	N Sample Size [Age in Years (y)]; Type of Study	Supplementation Time of LA, LA Dose and Associations with Other Antioxidants	Main Results
OBESITY AND CARDIOMETABOLIC DISEASES				
Yan [36]	Obesity	94 (18 - 60 y); randomized, double-blind, placebo control	1200 mg/d for 8 weeks	↓ Weight, BMI and WC; No improvement of OS markers (ox-LDL) and insulin resistance (HOMA-IR).
Koh [45]	Obesity	228 (18 - 65 y); randomized, double-blind, placebo control cross-over	1200 mg/d (a) or 1800 mg/d (b) for 20 weeks	↓ Weight and BMI (b); Did not alter TG and HDL serum levels; Did not alter BP
Witman [46]	Heart failure and heart transplant,	61; trial	First dose: 300 mg/d + vit C (500 mg) + vit E (200 IU) 2 h prior test; second dose 300 mg/d + vit C (500 mg) + vit E (400 IU) 1.5 h prior flow-mediated dilation test	Increase endothelium-dependent vascular function in subjects with > 14 y pos-heart transplant; Did not alter microvascular function
Wray [47]	CVD risk in elderly	6 (71 y - average); clinical trial, double-blind, balanced, cross-over	600 mg/d 3x per week for 6 weeks + Vit C (1000 mg) and Vit E (600 IU)	Annulled the positive effects of training on BP and vasodilation identified by serum markers.
McNeilly [48]	CVD risk in obese patients with glucose intolerance	24 (54 y - average); clinical, balanced, randomized trial	1 g/d for 12 weeks - with (a) or without exercise (b)	↓ Weight and WC (b); ↑ oxLDL (a). No improvement on serum lipid profile (a,b): HDL-c, TG, LDL-c; Did not alter serum inflammatory markers (a,b): CRP, homocysteine
Manning [49]	Metabolic Syndrome	160 (27 - 80 y); randomized, placebo control	600 mg/d for 1 y + Vit E	Did not alter glucose, insulin, HOMA-IR serum levels; ↓ non-esterified fatty acids in serum
Noori [50]	Diabetic nephropathy	34; randomized, placebo control	800 mg/d for 12 weeks + pyridoxine (80 mg/d)	↓ Urinary albumin, serum MDA and systolic blood pressure; ↑ nitric oxide, pentosidine and carboxymethyl lysine blood levels; did not alter serum endothelin-1, glucose and diastolic blood pressure
Lin [51]	Type 2 Diabetes	66; randomized, trial	For 6 months	Protected against glomerular podocyte injury by ↓ urinary levels of: MDA/Cr, 8-hydroxy-deoxyguanosine/Cr, albumin/Cr, podocalyxin/Cr; and increased of SOD and GPx activity
Bao [52]	Type 2 Diabetes	34 (34-66y); clinical trial	600 mg/d for 6 months	↓ Urinary MCP-1, TGF-b1, podocalyxin, nephrin and albumin to creatinine ratio; No alteration of fasting plasma glucose, HbA1c, urinary MCP-1/UCr, TGF-b1/UCr, PCX/UCr and nephrin/UCr
Gębka [53]	Type 1 Diabetes (a) Type 2 Diabetes (b)	12 (43 ± 12 y); 48 (59 ± 10 y); randomized, prospective.	300 mg/d for 3 months	↑ visual acuity (a,b), observed by contrast sensitivity examinations
Oliveira [54]	Type 2 Diabetes	102 (38 - 72 y); randomized, double-blind, placebo control	600 mg/d for 4 months + α-tocopherol	No improvement on serum lipid profile (TG, LDL-c, HDL-c, COL) and insulin sensitivity (HOMA-IR).
Porasuphatana [55]	Type 2 Diabetes	38 (44.5 ± 0.88); randomized, double-blind, placebo control	300/600/900 or 1200 mg/d for 6 months	All dosages were able to improve metabolic control and ↓ OS markers (↓ postprandial glycemia, HbA1c and TBARS).

(Table 1) contd….

Author	Clinical Situation	N Sample Size [Age in Years (y)]; Type of Study	Supplementation Time of LA, LA Dose and Associations with Other Antioxidants	Main Results
Gianturco [56]	Type 2 Diabetes	14; (>50 y); randomized, placebo control	400 mg/d for 4 weeks	↓ Concentration of reactive oxygen metabolites evaluated using a commercially available test ↑ HDL-c
Pop-Busui [57]	Type 1 Diabetes	44 (18-65 y); randomized, controlled trial	1200 mg/d + allopurinol (300 mg/d) + nicotinamide (1500 mg/d) for 24 months	Did not prevent progression of cardiovascular autonomic neuropathy; Worsened diabetic peripheral neuropathy (DPN). No beneficial effects on myocardial perfusion
Soare [58]	Healthy subjects	56 (38 - 75 y); controlled trial, double-blind	Pre-treatment with 600 mg/d for 6 months + AO ① Complex	No improvement on arterial stiffness, BP or metabolic variables involved with aging and CVD risk (serum levels of TNF-α, IL-6, CRP, HOMA-IR, glucose, TG, COL, LDL-c, carbonylated protein, AGEs)
PAIN AND INFLAMMATORY DISEASES				
Bae [59]	Rheumatoid arthritis	20; (52.1 ± 10.3 y.); randomized, double-blind, placebo control, cross-over	300 mg/d for 4 weeks + quercetin (500 mg or 166 mg) + Vit C (400 mg or 133 mg)	No alteration of serum inflammatory markers (IL-6, IL-1β, TNF-α, CRP) or disease severity
Mauro [60]	Chronic neck pain	96 (20 to 83 y); randomized, prospective	600 mg/d + SOD (140 IU) + physiotherapy *vs* Physiotherapy alone for 60 days	↓ Pain in the neck (lower scores on VAS and mNPQ) just like the group treated only with physiotherapy; Improved tolerance to physiotherapy
Battist [61]	Chronic neck pain	98 (72±10.9y); ± non-randomized, open-label	600 mg/d + SOD (140 IU) for 60 days	Improvement perceived pain and functional disabilities
Di Pierro and Settembre [62]	Peripheral neuropathy in anti-inflammatory treatment	135; randomized, controlled trial	400 mg/d alone or in combination with curcumin (400 mg /d) for 8 weeks	↓ Perception of pain (Scott-Huskisson scale and Short Form Health Survey). Enabled reduction in the dosage of anti-inflammatory drugs.
Ali [63]	Migraine	40 girls (16 to 20 y); randomized, prospective	300 mg/d alone or in combination with topiramate (50 mg/d) for 1 month	↓Frequency of migraine headaches (reported)
Patel [64]	Diabetic neuropathy	96; (54.5±8.3 y - carbamazepine group; 54.8±7,2 y - pregabalin group; 57.3±8 y - LA group); prospective, observational	200 mg/d *vs* carbamazepine or pregabalin for 6 months	↓ Number of patients having polyuria, polydipsia, patients having mild, moderate, severe and very severe pain; Improve symptoms of diabetic neuropathy (burning/aching pain in one or both lower limbs); ↓ glucose, postprandial glucose and HbA1c blood levels, however this result was lower than the pregabalin group. Decreased diabetic neuropathy examination score, however this result was lower than the pregabalin group. No improvement in nerve conduction velocity
Bertolotto and Massone [65]	Diabetic neuropathy	38 (68.2 ± 7.4 y.). Prospective, non-randomized, opened	600 mg/d + SOD (140 IU/d) for 4 months	Improved nerve conduction studies (motor and sensory) and pain perception (VAS and electroneurographic parameters)
Ziegler [66]	Diabetic polyneuropathy	454 (18 - 64 y.); randomized, double-blind, placebo control	600 mg/d for 4 y	Improved awareness and general pain in the lower extremities and reduced muscle weakness (several questionnaires)

(Table 1) contd….

Author	Clinical Situation	N Sample Size [Age in Years (y)]; Type of Study	Supplementation Time of LA, LA Dose and Associations with Other Antioxidants	Main Results
Gu [67]	Diabetic poly neuropathy	236; randomized, double-blind, placebo control	1800 mg/d for 12 weeks	↓ Symptoms reported for polyneuropathy and HbA1c serum levels Did not alter nerve conduction velocity
Pajardi [68]	Carpal Tunnel Syndrome (CTS) before and after surgical decompression of the median nerve	180 (57.9±14.8 y); prospective, observational	900 mg/d + curcumin (1500 mg) + B complex vitamin (a) *vs* 600 mg/d + curcumin (1000 mg) + B complex vitamin (b)	Decreased nocturnal symptoms scores (b) and lower number of positive Phalen's test (diagnostic test for CTS);
Di Geronimo [69]	Carpal Tunnel Syndrome (CTS)	102 (50.2 ± 14.3 y); prospective, nonrandomized, opened	600 mg/d + GLA (360 mg/d) + Selenium (50 μg/d) + vit E (7.5 mg/d) + B Complex *vs* B Complex for 3 months	Improved CTS symptoms, according to the BCTQ modified scale and the CTS electrophysiological scale
Ranieri [70]	Backache	203 (18-75y.); Observational cohort study	600 mg/d + GLA (360) + rehab exercises *vs* rehab exercises for 6 weeks	Improved symptoms and neuropathic deficits (VAS scores, Oswestry Low Back Pain Disability Questionnaire and Short Form Health Survey)
NEUROLOGICAL DISORDERS				
Khalili [71]	Multiple sclerosis	46 (18 - 50 y); randomized, double-blind, placebo control	1200 mg/d for 12 weeks	Improved inflammatory activity (↓: serum interferon gamma, intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and TGF-β); No alteration in serum TNF-α and IL-6.
Vidović [72]	Schizophrenia	18 (25 - 60 y); controlled trial	500 mg/d for 90 d	↓ Body fat, systolic blood pressure, serum uric acid, TBARS and AGE in control group but not in schizophrenic group; ↑ Glucose and LDL-c levels in control group; ↓ Glucose levels in schizophrenic group; ↑ AGE in schizophrenic group; ↓ serum HDL-c in schizophrenic group; No alteration in serum COL,TG and superoxide radical anion in both groups; ↓ SOD activity anion in both groups.
Shinto [73]	Alzheimer's disease	39 (>55 y); randomized, placebo-controlled, pilot trial	600 mg/d + w3 (DHA (2015 mg/d) + EPA (2925 mg/d)) for 12 months	No alteration in F2-isoprostane levels; Decreased in cognitive and functional measures
Galasko [74]	Alzheimer's disease	68 (50-85 y); randomized, double-blind, clinical trial	900 mg/d + α-tocopherol (800 IU/d) + vit C (500 mg/d) (a) *vs* CoQ10 (b) or placebo for 16 weeks	No alteration in cerebrospinal fluid biomarkers; Reduced OS in the brain by ↓ cerebrospinal fluid, F2-isoprostane levels
KIDNEY DISEASE				
Iciek [75]	Chronic renal failure on peritoneal dialysys	29 (56.93±13.06 y); trial	600 mg/d for 30 d	Improved redox profile by ↑ sulfane sulfur level (↑ability to covalently modify protein -SH groups and scavenging of free radicals)
Showkat [76]	Chronic renal failure on hemodialysis	10 (44.9 ± 9.1 y); open-label, crossover study	600 mg 30 minutes prior to iron administration.	Increased oxidative damage (↑ F2 isoprostane, lipid hydroperoxide
Safa [77]	Chronic renal failure on hemodialysis	61 (LA group - 59.3±10.47 y; placebo group - 55.20±13.43 y); randomized, double-blind, clinical trial	600 mg/d for 8 weeks	No alteration in serum IL-8 and TNFα,

(Table 1) contd….

Author	Clinical Situation	N Sample Size [Age in Years (y)]; Type of Study	Supplementation Time of LA, LA Dose and Associations with Other Antioxidants	Main Results
Ahmadi [78]	Chronic renal failure on hemodialysis	85 (20-60 y); randomized controlled trial	600 mg (a) *vs* vitamin E (400 IU) (b) *vs* LA and vitamin E (combined; 600 mg and 400 IU) for 2 months	No alteration (a,b,c) in: dietary intakes and anthropometric measurements; plasma level of MDA and high-sensitivity C-Reactive protein; or lipidic and glycemic profile; Improved in nutrition status evaluated by subjective global assessment (SGA) method (c); ↓ IL-6 level (a);
El-Nakib [79]	Anemia in patients with chronic renal failure in erythropoietin (EPO) treatment	44 (49.1±16.2 - treatment group; 64.2±14.4 control group); trial	600 mg/d for 3 months	↓EPO doses and EPO resistance index; No alteration on ox-LDL, IL-6, TNF-α and asymmetric dimethylarginine.
Khabbazi [80]	Chronic renal failure on hemodialysis	63 (22-79 y.); randomized, double-blind, placebo control	600 mg/d for 8 weeks	↓ Serum inflammatory activity (ultrasensitive CRP); No alteration on lipid peroxidation (MDA) and serum lipid profile (COL, LDL-c, HDL-c, TG).
Ramos [81]	Chronic renal failure (stage 3 to 4)	58 (64.5±8.8y - placebo group; 58.6±12.0 y - treatment group); randomized, double-blind, placebo control	600 mg/d + mixed tocopherols (666 IU) for 8 weeks	No alteration no OS serum markers (thiols and F_2-isoprostane groups) and inflammatory activity (IL-6 and CRP)
OTHERS				
Morawin [82]	Erythropoietin release	16 men (20.5± 6 y - LA group - 20.9±0.8y - control group); randomized, placebo control	1200 mg/g for 10 days prior to the exercise trial	Enhanced erythropoietin both before exercise and during recovery; ↑ H_2O_2 concentration 2-fold at pre-exercise but reduced changes in H_2O_2 and NO during recovery; Hemoglobin at pre-exercise, 20 min, and 24 h post-exercise; ↓ NO/ H_2O_2 ratio 2-fold at pre-exercise, 20 min and 24 h, but elevated it at 48 h after exercise; creatine kinase (compared to placebo group) during recovery. Prevented post-exercise changes in serum 8-isoprostanes, lipidic peroxidation and protein carbonyl levels, equal to placebo group;
Bharucha [83]	Heme oxygenase-1 in healthy subject	18 (23 - 63 y); randomized, double-blind, placebo control	Sodim salt of LA (1800 mg/d) + aspirin and simvastatin) for 7 d	Did not affect heme oxygenase-1 protein concentration or activity neither AST nor ALT serum levels.
Carter [84]	Iischemia-reperfusion in healthy subjects	20 (26.2±6.7 y); trial	300 mg/d + vit C (500 mg) + vit E (200 IU) 2h prior test (a); 300 mg/d + vit C (500 mg) + vit E(400IU) 1.5 h prior ischemia-reperfusion injury test (b); vs ibuprofen (c)	Did not affect endothelial dysfunction in brachial artery: did not preserve the flow-mediated dilation and did not improved the occlusive diameter low flow-mediated constriction).
Ives [85]	Chronic obstructive pulmonary disease	60; balanced, double-blind, placebo, crossover	300 mg/d + vit C (500 mg) + vit E (200 IU) 90 min prior test (a); 300 mg/d + vit C (500 mg) + vit E (400 IU) 60 min prior ischemia-reperfusion injury test of brachial artery flow-mediated dilation and carotide-radial pulse (b);	Improved vascular endothelial function *vs* placebo group; ↑ Global antioxidant capacity (assessed using the ferric reducing ability of plasma) but did not alter SOD level
Sun [86]	Macular degeneration	67 (50 - 75 y); trial	600 mg/d for 3 months	↑ SOD activity; No alteration in serum lipid profile (COL, TG, LDL, HDL) or prevention of lipid peroxidation (TBARS)

(Table 1) contd….

Author	Clinical Situation	N Sample Size [Age in Years (y)]; Type of Study	Supplementation Time of LA, LA Dose and Associations with Other Antioxidants	Main Results
Mainini [87]	Postmenopausal bone loss	44 (60.7±7.3 y - LA group; 59.5±6.5 y - control group); randomized, prospective	600 mg/d +vit C (60 mg/d) + vit E (10 mg/d) + selenium (5.5 mg/d) for 20 months	↑ BMD
Scuderi [88]	Postmenopausal dry eye syndrome	66; randomized, double-blind, placebo-controlled, crossover	+ phytoestrogens + eicosapentaenoic acid for 30 d	Improve the signs and symptoms of dry eye syndrome in postmenopausal women
Fogarty [89]	Exercise	12 (supplemented group mean of 23±6 y. *vs.* unsupplemented, mean of 27 ± 7 years); Randomized, single-blind, parallel	1000 mg/d for 14 days	Improved metabolic control and redox equilibrium (↑TAC serum - but not muscular; ↓ Serum lipid hydroperoxides and hydrogen peroxide) ↓ oxidative damage of mitochondrial DNA (8-OHdG) but not the muscle DNA (muscle tissue core biopsy)
Donato [90]	Exercise-induced brachial artery vasodilation	14 young (18-30 y) and 14 old (65-80 y); trial	2 doses: first = 300 mg + vit C (500 mg) + of vit E (200 IU) 2h before; second = 300mg + vit C (500 mg) + vit E (400 IU) 1.5 h before to graded handgrip exercise protocol	During handgrip exercise, brachial artery vasodilation in the old subjects was attenuated compared with that in young subjects; Restored exercise-induced brachial artery vasodilation
Georgakouli [91]	G6PD deficiency	16, 8 x 8 with normal levels with G6PD (33 y. - average) disability; trial	600 mg/d for 28 d	Improved redox equilibrium (↑ GSH and TAC, and ↓ TBARS serum levels); Did not change uric acid, hemoglobin and bilirubin serum levels Note: comparison made in relation to baseline (prior to supplementation)
Nachvak [92]	Down syndrome	93 (7-15y); randomized controlled trial	100 mg/d *vs* α-tocopherol (400 IU/d), for 4 months	Did not change TBARS levels; ↓ urinary 8OHdG concentrations
Lott [93]	Down syndrome and dementia	31 (± 50 y. - average); Randomized, double-blind, placebo control	600 mg/d + Vit C (200 mg) and vitamin E (900 IU) for 2 y	Did not improve any clinical variable or stabilized course of dementia
Martins [94]	Sickle cell anemia	60; randomized, placebo control	200 mg/d for 3 months	Improved patients with sickle cell lines oxidative profile (↑ catalase), but not in patients with sickle cell disease

AO① Resveratrol + quercetin + acetyl-L-carnitine + curcumin complex + pomegranate extract + fish oil + cinnamon bark + green/white and black tea complex + sesamin.
Legend: a, b = different treatments; ↑ = increased; ↓ = decreased; AGE = advanced glycation end products; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCTQ = Boston Carpal Tunnel Syndrome Questionnaire; BMI = body mass index; BMD = bone mineral density; BP = blood pressure; CoQ10 = co-enzyme Q10; COL = total cholesterol; Cr = creatinine; CRP = C-reactive protein; CVD = cardiovascular diseases; d = days; DHA = docosahexaenoic acid; DNA = deoxyribonucleic acid; EPA = eicosapentaenoic acid; GLA = gamma-linolenic acid; GPx = glutathione peroxidase; GSH = reduced glutathione; G6PD = glucose-6-phosphate dehydrogenase deficiency; IU = International Unit; HbA1c = glycosylated hemoglobin; HDL-c = high-density lipoprotein; HOMA-IR = the insulin/fasting glucose to assess insulin resistance; H_2O_2 = hydrogen peroxide; IL = interleukin; LDL-c = low-density lipoprotein; MCP-1 = monocyte chemoattractant protein-1; MDA = malondialdehyde; mNPQ = modified Neck Pain Questionnaire; NO = nitric oxide; oxLDL = oxidized low density lipoprotein; PCX = podocalyxin; SOD = superoxide dismutase; TAC = total antioxidant capacity; TBARS = Thiobarbituric acid reactive substances; TG = triglycerides; TGF-b1 = transforming growth factor-b1; TGF-β = transforming growth factor - β; TNF-α = tumor necrosis factor alpha; UCr = Urinary Cr; VAS = visual analogue scale; WC = waist circumference; 8OHdG = 8-hydroxy-2-deoxyguanosine, y = years

About atherogenic effect of LA observed in the study by McNeilly [48], this may be related, at least, in part, to the pro-oxidant action of DHLA, which had been already observed both *in vitro* (lipid peroxidation and reduction of Fe^{3+} to Fe^{2+}) [9], as *in vivo* (myocardial protein oxidation) [34]. When LA is administered in the diet, it accumulates in several tissues and a substantial part is converted to DHLA via a lipoamide dehydrogenase [179] and can be recycled back to lipoic acid [1]. This information is particurly important in view of the chemical natures of LA and DHLA which make them capable of participating in a variety of biochemical reactions based on redox activation [3].

One of the possible interferences in the studies is related to the variation of participants age. As an example, studies by Manning [49], Oliveira [54] and Pop-Busui [57] can be cited, where ages ranged between 27-80 years, 38-72 years and 18 - 65 years, respectively. Other interferences are dose and treatment time, which impair the comparison between studies, although, in all papers, safe LA doses (600 or 1200 mg/day) have been used [180].

Table 2. Oral supplementation action of lipoic acid (LA) alone or in association with other antioxidants in animal models: articles published from 2009-2014

Authors	Situation	Model / Age or Weight	Dose / Adm. Route / Time and Association	Main Results
OBESITY AND CARDIOMETABOLIC DISEASES				
Li [95]	HFD-induced Obesity	Male Zucker rats (5-6 weeks)	0.25% kg/kg diet for 30 d with normal diet (a) or with HFD	↓ mTORC1 activation in skeletal muscle ↑ Expression of markers of oxidative metabolism (ACC, COX IV, PPAR and PGC-1α)
Jang [96]	HFD-induced Obesity	Male C57BL/6J mice (4 week-old)	300 mg/kg + HFD (a); 300 mg/kg + HFD + swimming (b) x Betaine or L-carnitine with or without swimming; (all treatments by gavage) 9 weeks.	↓ Fat and body weight (b); blood glucose, TC, TG, leptin level (a,b). No alteration HDL-c and atherosclerosis index. ↑ Faecal TG and cholesterol levels
Carrier [97]	HFD-induced Obesity	Male Zucker rats (160g)	0.25% kg/kg diet for 30 d with HFD	Protected against body weight gain ↓ serum COL, non-HDL, LDL, HDL and insulin; hepatic total fatty acid an TG; mRNA expression of HMG-CoAr; hepatic lipogenic targets (Acetyl-CoA carboxylase - ACC and fatty acid synthase-FAS) ↑ HOMA-IR
Miao [98]	HFD-induced Obesity	Ovariectomized Wistar rats	12 weeks	Improved metabolic control and inflammatory activity; ↓ Weight, COL, LDL, leptin and IR serum levels, and IL-6 and TNF-α brain concentrations; ↑ Adiponectin, HDL-C serum levels and brain-derived neurotrophic factors expression, which are proteins that increase neurons survival.
Hontoria-Prieto [99]	HFD-induced Obesity	Wistar rats (6 weeks)	0.25% kg/kg diet for 56 days with normal diet (a) or with HFD (b)	Prevented weight gain (b);;↓ Weight gain (*), WAT gain (a,b); hyperinsulinemia, HOMA-IR (b) and relative adiponectin/WAT (a,b)
Seo [100]	HFD-induced Obesity	Male Sprague-Dawley rats (4 weeks)	0.25% kg/kg (a) 0.50% kg/kg (b) Diet	↓ Weight gain and liver weight, especially the group with 0.50% LA; Epididymal and intestinal fat (a,b); and atherosclerotic index (b); ↓ Serum levels of: total lipids and COL (b), TG (a,b); and LDL-C, the latter being compared both to the HFD group without LA, as well as the group with the standard diet; ↓ Hepatic total lipid concentration (a,b) and LDL-C (a,b), but not TG; ↑ HDL/LDL ratio (a,b)
Xu [101]	HFD-induced atherosclerosis	Male Sprague- Dawley rats (150 - 170 g)	LA + Linseed (8 g/kg) oil for 10 weeks	Improved metabolic control, OS and inflammatory activity; ↑ Hepatic SOD, catalase and GPx and HDL-C/LDL-C serum, and ↓TG, COL, LDL-C, IL-6, CRP serum levels and hepatic lipid peroxidation (TBARS).
Yi [102]	HFD- and medications induced Hypertriglyceridemia	Obese male Zucker rats (7 weeks)	200 mg/kg (diet) for 2 weeks	Improved metabolic control ↓ TG serum levels, abdominal adipose tissue, enzymes involved in *de novo* fatty acid and TG syntheses gene expression; ↑ Expression of proteins involved in lipid and glucose metabolism.
Butler [103]	Hypertriglyceridemia	Obese male Zucker rats (5 weeks)	0.24% kg/kg (diet) for 5 weeks	Did not alter glycemia or insulinemia; mediated hepatic glycogen storage. ↓ Hepatic TG (by inhibiting *de novo* synthesis of TG and hepatic TG secretion).

(Table 2) contd….

Authors	Situation	Model / Age or Weight	Dose / Adm. Route / Time and Association	Main Results
Matsumoto [104]	Cardiovascular Disease	Male Wistar rats (10 weeks)	0.16% kg/kg (diet) for 14 weeks + α-tocopherol (1000 IU) with (a) and without exercise (b)	↓ Inflammatory activity in endothelial cells of the left ventricle and the coronary artery (↓ IL-6 expression (a,b)) Differently regulated genes involved in the synthesis of endothelial cells; ↑ Expression of genes involved in CVD (b), which was eliminated by exercise and antioxidant defense (b).
Yang [105]	Insuline resistance HFD-induced	Male C57BL/6J mice (6 weeks)	HFD + 100 mg/kg (a) or 200 mg/kg (b) for 24 weeks	Prevented HFD-induced-NAFDL (↑ AKT phosphorylation levels and enhanced GSK3β phosphorylation) ↓ Body weight, liver weight, blood glucose level, water intake, BMI and abdominal circumference; insulin resistance, blood glucose levels; and hepatic glucose production capacity (a.b); ↑ HOMA index and glycolytic gene activity levels and expression levels (a,b).
Naito [106]	Genetical model of Diabetes	Male type 2 diabetic KKAy mice (4 weeks)	0.25% kg/kg alone (a) or combined with + γ-cyclodextrin (b) (by diet). 31 days	No alteration body weights and glucose blood levels or GLUT4 expression (a, b); ↓ HbA_{1c} serum levels(b) ↑ AMPK levels in the skeletal muscle, the master regulator of cellular energy homeostasis
Dominguez [107]	Medication-induced Diabetes	Male Sprague-Dawley rats (12 weeks)	0.25% kg/kg + Ilepatril (500 mg/kg) + Fidarestat (3 mg/kg) + Menhaden oil (25% kcal/kg) (along with diet) (a) for 6 weeks x inhibition of neutral endopeptidase (b) and insulin therapy (c).	Prevented loss of nerve conduction velocity and corrected increases of immunoreactivity for neuropeptide Y, tyrosine hydroxylase and somatostatin (a,b,c); ↓ Levels of IL- 1β, granulocyte colony-stimulating factor and MMP-2 in bone marrow supernatant (a,b,c); ↓ Expression of NOX-2, NOS-2 and NF-κB1 in bone marrow progenitor cells (a,b,c).
Jin [108]	Medication-induced Diabetes	Male Sprague-Dawley rats (6 - 8 weeks)	100 mg/kg/day alone (a) or combined with pioglitazone (b) (by diet), 24 weeks	Did not alter fasting blood glucose and HbA1c levels; ↓ TG and TC levels (a,b); ↑ HDL-c levels (a,b); SOD from blood and sciatic nerve (a,b); Enhanced tactile withdrawal threshold assessed by response to a light touch with von Frey filaments (b); Improved skin blood flow at resting state (b); Preserved peripheral nerve fiber (b); Increased endoneurial area and fewer nerve fibers with a degenerated myelin sheath (b).
Kowluru [109]	Streptozotocin-induced diabetic	Male albino rats (220-225 g)	750 mg/kg + multi-nutritional supplements containing carotenoids (diet)	Improved retinal function; ↓ ROS levels Prevented damage to mitochondrial DNA involved in electron transport chain complex I; and the increased capillary cell apoptosis and vascular pathology
Saraswathi [110]	Medication-induced Diabetes	Male albino rats (160-180 g)	100 mg/kg/d (gavage) for 30 d	Did not prevent weight gain in diabetic rats; ↓ Glucose and insulin serum levels; ↓ Mitochondria skeletal muscle ROS generation and OS markers (↓ Protein carbonylation proteins, LPS, TBARS, and ↑ SOD, catalase, GPx, GR, Vit C and Vit E; ↑ Urea synthesis (↑ isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, succinate dehydrogenase and malate dehydrogenase)

(Table 2) contd….

Authors	Situation	Model / Age or Weight	Dose / Adm. Route / Time and Association	Main Results
Ramasamy [111]	Medication-induced Diabetes	Male albino rats (160-180 g)	100 mg/kg/d (gavage) for 30 d	↓ Skeletal muscle mitochondria ROS generation and OS markers (↓ TBARS, Cyt c in the cytosol - indicator of apoptosis - and carbonylated proteins; ↑ SOD, catalase and GPx); Aid in maintaining the mitochondrial membrane potential.
Midaoui [112]	Glucose ingestion-induced Diabetes	Male Sprague-Dawley rats (23 days / 50 to 75 g)	% 0.1 kg/kg diet for 12 weeks	Normalized/attenuated the production of aortic and hepatic $O_2^{\cdot-}$ ↓ Hepatic expression of PPAR-α; improved metabolic control; ↓ SBP, hyperinsulinemia, hyperglycemia, and insulin resistance
Yi [113]	Medication-induced Diabetes	Male C57BL/6 mice apoE $^{-/-}$ (12 weeks)	200 mg/kg (diet) + HFD for 16 weeks	Improved glycemic control, OS and inflammatory activity ↓ Glycemia, ↑ Erythrocyte GSH, SOD activity in the renal cortex and renal expression of GPx, SOD2; ↓ Serum TBARS, urinary 8-isoprostane, TBARS and renal cortex AGE and RAGE and IL-6 renal expression; Prevented renal damage (↓ kidney weight/body weight, albuminuria and matrix mesangial expansion). Did not alter blood pressure
Yang [114]	HFD-induced NAFLD	Male C57BL/6J mice (6 weeks)	HFD + 100 mg/kg (a) or 200 mg/kg (b) for 24 weeks	↓ Visceral fat mass (a,b), appetite (a,b), weight loss (a,b), hepatic triacylglycerol content (a,b), perirenal fat weight (a), LDL-c and glucose blood levels (a). ↑ HDL-c (a)
Kathirvel [115]	HFD-induced NAFLD	Male mice 75% Balb/c and 25% B6D2F2 (4 weeks)	0.1% g/mL LA + 0.2% (ALC) in drinking water for 6 months	Did not reduce body weight and liver weight; did not improve insulin resistance (HOMA-IR); did not reduce hepatic lipid peroxidation (MDA); ↓ Liver damage (↓ ALT and AST serum levels; ↑ number and function of liver mitochondria - ↑ Concentration of carbamoyl phosphate synthase 1 and size of liver mitochondria)
Valdecantos [116]	HFD-induced NAFLD	Male Wistar rats (6 weeks)	0.25% kg/kg diet	Prevented the increase of liver weight caused by HFD; Improved metabolic control (↓ Caloric intake, HOMA-IR) Improved hepatic metabolism and reduced intra-hepatic fats (↓ TG and intra-hepatic MDA, ALT and AST serum, hepatic vascular wall thickening, lipogenesis proteins expression; ↑ β-oxidation and proteins of citric acid cycle expression) ↓ Hepatic lipid peroxidation (MDA); ↑ Mitochondrial generation of $O_2^{\cdot-}$ and ↓ H_2O_2
Min [28]	Choline deficiency-induced NAFLD	Male C57BL/6 mice (8 weeks)	% 0.5 kg/kg diet	Improved hepatic metabolism and reduced intra-hepatic fats (↓ TG, inflammation and hepatic OS through inhibition of CYP2E1 and decreased of NF-kB expression plus TG, ALT and AST serum levels)
AGING				
Keith [117]	Age-associated metabolic disorders	Male Fischer rats (24 months)	0.2% kg/kg diet for 2 weeks	Caused a significant phase-shift in the expression patterns of the circadian clock; Altered the oscillatory patterns of clock-controlled proteins associated with lipid metabolism (↑ PPAR-α and ↓ acetyl-CoA carboxylase and fatty acid synthase)

(Table 2) contd….

Authors	Situation	Model / Age or Weight	Dose / Adm. Route / Time and Association	Main Results
Ajith [118]	Brain energy status	Male Wistar rats (24 months)	1.2 mg/mL (a) or 23.5 mg/mL of Palladium-LA complex (b)	↑ Mitochondrial ATP levels in the brain (enhancing effect on the Krebs cycle dehydrogenase and the activities of complexes I, III, and IV) (a,b).
Thakurta [119]	Learning ability and memory retention	Charles Foster albino rats (22-24 months) rats supplemented or not x Young rats (4-6 months)	3 mg/100 g + NAC (50 mg/100 g) + α-tocopherol (1.5 mg/100 g) (along with diet) for 4-6 weeks	↓ Cerebral lipid membrane (4-HNE) damage; Prevented learning disabilities; Improved memory performance
Thakurta [30]	Brain aging	Charles Foster albino rats (22-24 months) rats supplemented or not x Young rats (4-6 months)	3 mg/100 g + NAC (50 mg/100 g) + α-tocopherol (1.5 mg/100 g) (along with diet) for 4-6 weeks	↓ Cerebral H_2O_2 formation and inflammatory activity (↓ mitochondrial NADPH activity, NF-KB expression and the IL-1β, IL-6 and TNF cerebral concentrations)
Sinha [120]	Risk of Alzheimer's	Male Wistar rats (22-24 months)	30 mg/kg (diet) + NAC + α-tocopherol (diet) for 18 months	Prevented brain changes associated with Alzheimer's disease (↓ Homocysteine brain concentrations and prevented the reduction of glutathione)
Wang [121]	Energy metabolism	Male C57BL/6 mice (24 months)	0.75% kg/kg diet	Improved body composition (↑ muscle and bone mass); Improved glucose metabolism (↑ glucose utilization by respiratory quotient increased), Insulin sensitivity (during a glucose tolerance test) and GLUT-4 gene expression skeletal muscle).
Sudheesh [122]	Cardiac OS	Male Wistar rats (24-26 months)	0.05 mL/kg of LA + complexed palladium (POLY-MVA ®) [¥]	Improved redox imbalance in the myocardium (↑ Catalase and GPx, and ↓ MDA)
Someya [123]	Hearing loss due to aging	Male and female mice $Bak^{-/-}$, $Bax^{-/-}$and C57BL/6 (4 months)	150 mg/d (diet) for 9 months	Reduced hearing loss by improving redox imbalance and suppressing the expression in the Bak cochlear region
Sudheesh [124]	Cardiac energy metabolism	Male Wistar rats (24 months)	5 mg/kg associated (a) or complexed LA + palladium complex (Poly-MVA®) [¥] (b) (Gavage) for 30 d	Improved cardiac energy metabolism (↑ Citric Acid Cycle enzyme activity (a, b) and mitochondrial respiratory complexes (a,b)
NEUROLOGICAL DISORDERS				
Sancheti [125]	Alzheimer's disease	Triple transgenic mouse model of Alzheimer (7 months)	0.23% R-sodium lipoic acid (water) for 4 weeks	↓ Glucose hypermetabolism (brain)
Villasana [126]	Associative and spatial memory	C57BL/6 irradiated or not with ^{56} Fe (6 to 9 months)	0.165% kg/kg diet for 6 months	Did not affect behavior of the exploratory type the exploratory behavior or anxiety; Impaired object recognition and conditioned fear; Prevented damage induced by radiation in the retention of memory
Cui [127]	HFD-induced cognitive impairment	Male KM mice (5 weeks)	% 0.1 kg/kg diet for 10 weeks	Reduced cognitive memory deficit; Improved OS in the hippocampus (↑: catalase, GSH, GPx, TAC and ↓: MDA)
Araújo [128]	Stereotaxic-induced Parkinson's disease	Male Wistar rats (250-300 g)	100 mg/kg (a) + levodopa (b); 200 mg/kg/d (c) + levodopa (d) (gavage) for 2 weeks	Increased rotational behavior and increasing locomotor activity (a,b,c,d); Improved redox profile (↓ TBARS in cortex (a,c,d), hippocampus (a,b,c,d) and striatum (a,b,c,d)).
Takechi [129]	SFA diet-induced disturbances in blood-brain barrier function	Wild-type C57BL/6J female mice (6 weeks)	% 0.2 kg/kg diet *vs* garlic extract-aged, niacin or nicotinamide	No alteration on non-esterified fatty acid levels (contrarily niacin and nicotinamin groups); Improved blood-brain barrier integrity and suppressed expression of GFAP and COX-2 (such as niacin and nicotinamin groups);

(Table 2) contd….

Authors	Situation	Model / Age or Weight	Dose / Adm. Route / Time and Association	Main Results
Abdin & Sarhan [130]	Medication-induced Parkinson's disease	Albino mice (20-22 weeks)	100 mg/kg/d (gavage) for 3 months	Prevented the neurological damage (myelin sheath and neuronic destruction) characteristic of Parkinson's Disease
Suchy [131]	Cognitive performance	Male C57BL/6 mice (9-12 months) or ApoE$^{-/-}$ mice	200 mg (diet) + acetyl-L-carnitine + glycerophosphocholine + DHA + phosphatidylserine for 4 weeks; associated or not to a diet deficient in vitamins and minerals	↓ redox imbalance (TBARS) in brain (normal mice and ApoE$^{-/-}$); Improved cognitive performance (normal mice with a deficient diet)
Thaakur and Himabindhu [132]	Haloperidol-induced tardive dyskinesia	Male Wistar rats (150 to 200 g)	25/50/100 mg/kg (gavage) for 21 d	A dose of 100 mg/d minimized tardive dyskinesia
Erşahin [133]	Subarachnoid Hemorrhage-induced oxidative brain injury	Male Wistar rats (300 to 350 g)	100 mg/kg (gavage) for 2d	↑ Brain GSH, Na+, K+-ATPase; ↓ DNA fragmentation ratios and MDA levels and MPO activity Improved brain edema, blood-brain-barrier permeability and neurological scores
CANCER				
Taniai [134]	Ochratoxin-induced renal carcinogenesis	Male F344/NSlc rats (4 weeks)	% 0.2 kg/kg (diet) for 5 weeks	↓ Body weight; ↑ Relative weight of the kidneys; Did not alter the expression of antioxidant enzymes (Ochratoxin did not cause renal damage through OS)
Trevisan [135]	Neuropathy Chemotherapy-Induced (bortezomib or oxaliplatin)	Male C57BL/6 mice (25 - 30g)	100 mg/kg/d (gavage) for 7 d	Reduced Chemotherapy adverse effects (↓ hyperalgesia and impeded mechanical hypersensitivity)
Fujii [136]	Thioacetamide-induced liver carcinogenesis	Male F344/NSlc rats (5 weeks) hepatectomized	% 0.2 kg/kg diet for 6 weeks	Showed hepatoprotective effect (↓ Liver carcinogenic activity by thioacetamide)
Al Abdan [137]	Implantation of neoplasic cells i.p-induced liver carcinogenesis	Female Swiss albino mice (20-25 g)	50 mg/kg/d for 30 d	Improved hepatic control (↓Ascites and ↑ Survival)
INFLAMMATORY DISEASES				
Trivedi and Jena [138]	Ulcerative colitis DSS-induced	Male Swiss mice (25 to 28 g)	20/40/80 mg/kg/d for 14 or 28 days (gavage)	↓ Intestinal damage; Improved redox balance and colonic inflammatory activity: ↓ TBARS, LPS, MPO, IL-17 and IL-6; ↑ GSH; ↑ Nrf2 and NQO-1 (anti-inflammatory) expression and ↓ NF-kB and STAT3 (pro-inflammatory) expression: ↓ Fibrosis and DNA damage (comet assay)
Cui [139]	HFD-induced splenic inflammatory response	Male C57BL/6 mice (age not reported)	% 0.1 kg/kg in HFD diet for 10 weeks	Improved redox balance (↑ SOD, catalase, TAC, GSH/GSSG ratio, GSH-GPx and ↓ MDA- serum and spleen) Improved inflammatory response (↓ Splenic B cell apoptosis; ↑ B cells serum and splenic levels)
Cui [139]	Splenic inflammatory response	Male C57BL/6 mice (4 weeks)	% 0.1 kg/kg in HFD diet for 10 weeks	Improved splenic redox balance (↑ GSH/GSSH ratio; and ↓ ROS and MDA); ↑ anti-apoptotic proteins expression.
Hah [140]	Collagen induced Rheumatoid arthritis induced collagen	Male DBA/1 mice (7 - 9 weeks)	0.1% or 0.5% kg/kg diet for 49 d	Improved clinical signs and reduced the inflammatory response ↓ IL-1β, TNF-α, sRANKL in synovial tissues, and ↓ IL-1β, TNF-α serum levels

(Table 2) contd….

Authors	Situation	Model / Age or Weight	Dose / Adm. Route / Time and Association	Main Results
OTHERS				
Liu [141]	Muscle atrophy induced by unloading mitochondrial dysfunction	Sprague-Dawley rats (66 weeks)	50 mg/kg/d + ALC (100 mg/kg/d) + CoQ10 (5 mg/kg/d) + Hydroxytyrosol (10 mg/kg/d) (diet) for 4 weeks	Promoted the recovery of neuromuscular function and accelerated the reloading-induced muscle gain; Preserved/promoted gain of cross-sectional area; Blunted protein degradation and muscle atrophy (↓ mRNA levels of MuRF-1 and atrogin-1 and the protein expression level of FOXO3); Maintained the activities of mitochondrial complex I and II and recovery of mitochondrial membrane integrity; Blocked apoptotic signaling in the soleus by reduced cleavage and activity of caspase-9 and caspase-3; Improved redox profile (increased GSH and reduced MDA levels and inhibition of MAPK signaling)
Ali [142]	Thioacetamide-induced liver cirrhosis	Male Wistar rats (140-180 g)	200 mg/kg/d (orally) vs curcumin or silybin-phytosome. 7 weeks	↓ ALT, AST, LDH, GGT and bilirubin levels; ↑ Albumin, TG and CT levels; reversed the OS (↑ GSH and ↓ MDA and carbonyl protein liver levels); ↓ more effectively serum TGF-b1 level and genes expression of liver fibrosis (α-smooth muscle actin and heat shock protein-47)
Al-Rasheed [143]	Zinc oxide nanoparticles (ZnO-NP)-induced liver damage	Wistar rats (180-200 g)	200 mg/kg/d + ZnOPs: 600mg/kg/d (a) or 1g/kg/d (b) for 3 weeks vs. vit E treatments	↓ Serum glucose, ALT, TNF-α, IL-6, CRP and IgG (a,b); hepatic caspase 3 (a,b; but less intensely than vit. E treatments); ↑ H epatic GSH (a,b); Protect DNA damage (liver) (a,b); Improved histopathological injury, observed by miniml hepatocytes with karyolysis and pyknotic nuclei (a,b; but more intensely than vit E treatments); Decreased liver collagen deposition (a,b)
Di Curzio [144]	Kaolin-induced hydrocephalus	Sprague-Dawley and Long Evans rats (21 days)	DHLA (20 and 100 mg/kg) + Alpha-tocopherol (50 and 250 mg/kg) + CoQ10 (40 and 200 mg/kg) + GSH (20 and 100 mg/kg)	No consistent evidence for normalization of behavior abnormalities (ambulation, water maze, ladder test); No effect on corpus callosum thickness No effect on lipid peroxidation in the parietal cerebrum or total antioxidant capacity
Lebda [145]	Acrylamide-induced testicular damage	Male rats (210 ± 7 g)	1% kg/kg diet for 28 d	No alteration on serum total testosterone, progesterone and estradiol levels Increased redox profile in testis and epididymis (↓ MDA and ↑ GST, GPx and GR)
El-Beshbishy [146]	Bi-n-butyl (BNBP)-induced testicular damage	Male rats (170 ± 10g)	20 mg/kg 24 h prior to the administration of BNBP, orally, for 14 d	↑ Testicles weight, cauda epididymal sperm counts and sperm motility percentage; serum follicle stimulating hormone, testosterone and total antioxidant status; testicular catalase, SOD and GR. ↓ Testicular LPO, LDH
Jana [147]	Intensive swimming-induced germ-cell death	Male Wistar Rats (3-4 months)	3 mg/100 g (gavage) + NAC (50 mg/100 g) for 1 week before and for 8 weeks during the exercise period	Protective role against exhaustive exercise-induced dysfunctions of testicular androgenesis (↓ expression of gene involved with reduction of testosterone levels); ↓ ROS generation; improved redox profile just in control group (without intensive exercice); ↓ Intracellular ATP Levels, caspase 3 activation and DNA damage in testicular tissue.

(Table 2) contd….

Authors	Situation	Model / Age or Weight	Dose / Adm. Route / Time and Association	Main Results
Chen [148]	Induced Corneal and Conjunctival Degeneration	Female CBA mice	1 (a), 10 (b), and 100 (c) mg/kg/d (diet) for 10 days	Ameliorated corneal damage (b,c); Reduction polymorphonuclear leukocyte infiltration and matrix metalloproteinases-9 expression(b,c); Ameliorates photophobia and aqueous tear reduction (b,c); Decreased MDA accumulation and proinflammatory factors (TNF-a and IL-6).
Andrade [149]	Bilateral ovariectomy-inducced dry eye	Wistar rats (3 months)	LA group (80 mg/kg/d) vs DHA group (1g/kg/d + 0.2 g/kg/d of EPA) vs EPA group (1g/kg/d + 0.2 g/kg/day of DHA) - diet	Like the EPA group, the LA group reduced progesterone serum levels; Restored tear production assessed by the Schimer assay; ↑ Cornea GPx but not SOD and total aconitase activities; Did not alter lacrimal gland Vit C and GSH/GSSG levels; Restored cornea nitrite and nitrate levels; ↑ Cornea protein carbonylation; ↓ Lacrimal gland lipid peroxidation (MDA), in comparison to the DHA group.
Sachdeva [150]	Toxicity - exposure to tungsten	Male Wistar rats (100 - 120g)	LA (a) (61.9 mg/d) vs quercertin (b) (90.7 mg/d) / NAC (c) (49 mg/d) / naringenin (d) (91.7 mg/d) - oral	Improved weight gain caused by poisoning (a,c,d); ↑ δ-aminolevulinic acid dehydratase Serum activity (a,c) Minimized blood ROS formation (a,b,c,d); ↑ catalase but not GSH, SOD and TBARS serum activities; Improved hepatic redox profile (↓: ROS (a,b,c,d) and TBARS (a,c), GSH/GSSG ratio (a,b,c,d) and TBARS (a,c)
Ozler [151]	Surgical procedure-induced intra-abdominal adhesion	Male Sprague-Dawley rats (12 weeks)	100 mg/kg (gavage) for 15 d starting after 25 d after intra-abdominal adhesion	Reduced intra-abdominal adhesion and redox imbalance (macroscopic analysis and ↓ tissue hydroxyproline and MDA)
Dwivedi [152]	Pesticide poisoning (arsenic and DDVP)	Male Wistar rats (110-120 g)	50 mg/kg	Improved pesticides toxic effects on the redox imbalance (↑ SOD, catalase, GST, and GPx and ↓: TBARS, in both, blood and brain); Improved hematological parameters (HB, HCT, PLT) and serum markers of liver (↓ ALT and AST)
Derin [153]	Sodium metabisulfite poisoning	Male Wistar rats (5 months)	100 mg/kg/d (gavage) for 5 weeks	Improved cerebral redox imbalance (↑ GPx, and ↓ TBARS) and in the retina (↓ TBARS); reduced the effect of metabisulfite on the visual evoked potential
Cadirci [31]	Sepsis-induced acute lung injury	Male Wistar rats (16 weeks)	200 mg/kg (gavage) - acute dose	Reduced serum inflammatory activity (↓ TNF-α, IL-6, MPO and LPO) and pulmonary inflammatory activity (↓ NF-kB)
Xiao [154]	HFD-induced malabsorption of calcium	Male C57BL/6 mice (5 weeks)	% 0.1 kg/kg by diet for 9 weeks	Improved redox balance (↑ SOD, catalase, TAC and GSH/GSSH ratio; and ↓ TBARS - serum and duodenal levels); Improved calcium balance (↑ intestinal absorption and BMD)
Xiao [155]	HFD-induced low bone mineral density	Male C57BL/6 mice (4 weeks)	% 0.1 kg/kg by diet for 9 weeks	Improved bone redox imbalance (↑ SOD, TAC and GPx, and ↓ MDA). Stimulated bone mineralization (↑ osteocalcin, alkaline phosphatase 1 and collagen 1α1, and ↓ neurofibromastose 1 expression)

(Table 2) contd….

Authors	Situation	Model / Age or Weight	Dose / Adm. Route / Time and Association	Main Results
Aydin [156]	Femoral fracture	Female Wistar rats (240-260 g)	25 mg/kg/d (a) or 50 mg/kg/d (b) by gavage for 30 d	↓ Serum osteocalcin, osteopontin, TNF-α, and IL-6 (b); Improved fracture healing, both treatments (a,b), but more intensely the b group;↑ Osteoclast number (a,b), but more intensely the b group; mRNA level of TGF-β (b); callus density (a,b); BMD (a,b); resistance to bone failure (a,b); resistance to bone deformation (b)
Inman [157]	Glaucoma	Mutant DBA/2J mice: 6 months - intervention group; or 30 d - Prevention group	0.06% kg/kg (diet) for 4 months (a); 0.1% kg/kg by diet for 11 months (b)	Improved redox profile (↑ antioxidant *(*Cp, Ho-1*)* and ↓ pro-oxidant (NOS-*2)* genes expression); Improved protection of retinal ganglion cells (↑ GFAP expression); ↓ Oxidative damage (proteins - nitrated proteins-, lipid peroxidation - MDA - and retinal DNA damage)
Asci [158]	Amikacin-induced nephrotoxicity	Female Wistar rats (250-300 g)	100 mg/kg/d (gavage) for 5 d	Improved redox profile in kidney (↓ MDA and ↑ catalase activity); Improved renal fuccion (↓ serum urea, renal damage indicators and creatinine);; ↓ Kidney damage by decreased tubular dilatation, cortex and medulla hemorrhage and proximal and distal tubular degeneration.
Pradhan [159]	Acetaminophen-induced nephrotoxicity	Male Wistar rats (100 g ± 15 g)	50 mg/kg/day or 100 mg/kg/d (diet)for 25 d	Improved redox balance (↑ serum TAC and renal SOD; ↓ renal MDA);
Brown [160]	Radiation	C57BL/6 mice (7-8 weeks)	100 μg/g + L-selenomethionine (0.12 μg/g) + sodium ascorbate (19 μg/g) + NAC (51 μg/g) + α-tocopherol succinate (8.6 μg/g) and Co Q10 (51 μg/g) (diet) for 30 d	Provided significant mitigation from radiationinduced lethality ↑ numbers of spleen colonies and blood cells
Mignini [161]	Cypermethrin-induced OS	Male Wistar rats (150-170 g)	53.14 mg/kg/d (diet) for 2 months	No alteration body weight, NO plasma level and protein carbonylation; Improved redox profile (restored SOD, catalase and GPx activities); Protective against lipid peroxidation such as placebo group.
Abdel-Hafeez [162]	Schistosoma mansoni-induced fibrosis	Male Balb/c mice (18-22 g)	400 mg/kg/d (gavage) for 20 months + praziquantel	Reduced worm burden, egg count, and granuloma size.

¥- Simplified composition POLY-MVA®: palladium complex + LA (1:1) + thiamine + *N*-acetylcysteine + riboflavine + *N*-formyl methionine + cyanocobalamine + rhodium + molibdenium + sodium chloride

Legend: a, b, c, d = different treatment models; ↑ = increased; ↓ = decreased; ACC = acetyl CoA carboxylase; AGE = advanced glycation end products; ALC = acetyl L-carnitine; AMPK = 5' adenosine monophosphate-activated protein kinase; ApoE $^{-}$ = knockout mice for apoprotein E; Akt = protein kinase B; ALT - alanine aminotransferase; AST = aspartate aminotransferase; ATP = Adenosine triphosphate; ATPase = adenylpyrophosphatase; BAX = protein x associated with BCL-2; Bak = Homologous Antagonist-Killer Protein Bcl-2; BMD = bone mineral density; BMI = body mass index; Cyt c = cytochrome complex; CoQ10 = co-enzyme Q10; COL = total cholesterol; COX IV = cytochrome c oxidase IV; COX-2 = cyclooxygenase 2; Cp = ceruloplasmin; CYP2E1 = cytochrome P450 2E1; CRP = C-reactive protein; CVD = cardiovascular disease; DDVP = 2,2-dichlorovinyl dimethyl phosphate; DHA = docosahexaenoic acid; DSS = dextran sulfate sodium; DNA = Deoxyribonucleic acid; EPA = eicosapentaenoic acid; FOXO3 = forkhead box O3; GFAP = Glial fibrillary acidic protein; GGT - gamma glutamyltransferase; GLUT4 = Glucose transporter type 4; GPx = glutathione peroxidase; GPC = glycerophosphocholine; GR = Glutathione reductase; GSH = reduced glutathione; GSK3β = Glycogen synthase kinase 3β; GST = glutathione-S-transferase; GSH/GSSG = reduced glutathione/oxidized glutathione ratio; H_2O_2 = hydrogen peroxide; HCT = hematocrit; HDL-C = high density lipoprotein; HFD = high fat diet; HB = hemoglobin; HBA1c = glycosylated hemoglobin; IU = international unit; IL = interleukin; IR = insulin resistance; IgG = immunoglobin G; HO-1 = Heme oxygenase-1; HOMA - IR = the insulin/fasting glucose to assess insulin resistance; HMG-CoAr = 3-hydroxy-3-methylglutaryl-coenzyme A reductase; LDL-C = low-density lipoprotein; LDH = lactic dehydrogenase; LPO = lipoperoxidase; LPS: lipopolysaccharide; MAPK = mitogen-activated protein kinase; MDA = Malondialdehyde; MMP2 = matrix metalloproteinase-2; mTORC1 = Mammalian target of rapamycin complex 1; mRNA = messenger Ribonucleic acid; MPO = myeloperoxidase; MuRF-1=muscle ring finger 1; Na+/K+-ATPase = sodium-potassium pump; NADPH = Nicotinamide adenine dinucleotide phosphate reduced; NAC = n-acetylcysteine; NAFLD = non-alcoholic fatty liver disease; NF-kB = (nuclear factor kappa-light-chain-enhancer of activated B cells); Nrf2 = nuclear erythroid 2-related factor 2; NOS-2 = Nitric oxide synthase 2; NOX-2 = nicotinamide adenine dinucleotide phosphate-oxidase 2; NQO - 1 = quinone oxidoreductase-1; NOS-2 = Nitric oxide synthase inducible; $O_2^{\cdot-}$ = superoxide radical anion; OS = oxidative stress; PLT = Platelet; PPAR-α = peroxisome proliferator-activated receptor-α; PGC-1α = PPAR gamma coactivator 1-alpha; RAGE = receptor for advanced glycation end products; ROS = reactive oxygen species; SOD = superoxide dismutase; STAT 3 = Signal transducer and activator of transcription 3; sRANKL = soluble receptor activator of NF-κB; SBP = systolic blood pressure; SFA = saturated fatty acids; TG = triglycerides; TGFb1 =transforming growth factor-b1; TC = total cholesterol; TNF-α = tumor necrosis factor alpha; ; TAC = total antioxidant capacity; TBARS = thiobarbituric acid reactive substances; WAT = white adipose tissue; 4-HNE = 4-Hydroxynonenal; 8OHdG = 8-hydroxy-2-deoxyguanosine

Besides the difference between species (humans and rats/mice), another factor that might be influencing the results with higher positive impact in animals can be the tissue/fluid analysis of the biomarkers. Humans, almost all the studies used physical tests and serum or urinary markers, in animal tests, serum and tissue measurements were performed, beyond gene expression, i.e, a higher variety of biomarkers was used. Thus, many of the experimental studies were able to identify changes in the concentrations of these markers in blood and the analyzed tissues themselves [139,152, 154].

4.3. LA Oral Administration Improves Various Markers for Redox Imbalance in Aging

In animal models, supplementation with LA led to attenuation of RONS [30] that are involved in the reduction of lifespan. It has been shown to reduce accumulation of macromolecules' damage [181], mitochondrial dysfunction and some neurodegenerative disorders [182], as well as in the increase of redox compounds gene expression, which may lead to the prolongation of life [181]. However, in the only study conducted in humans [86], this antioxidant just provoked the increase of superoxide dismutase (SOD) levels.

Also in animal models, the LA supplementation associated with acetyl-L-carnitine for one month, inhibited prejudicial changes in the rats myocardium, such as generation of pro-oxidants and oxidative damage to deoxyribonucleic acid (DNA) and lipids. However, these two agents combined increased oxidative injury in liver tissue, represented by increased of MDA (malonaldehyde) levels [115].

The LA supplementation associated with palladium alone [118] or combined with other substances (see composition in the footnote of Table **2**) [122,124], was seen to be effective in improving the redox profile [122], cardiac energy metabolism [124] and mitochondrial metabolism in brain [117]. Another example of an effective combination was LA associated with α-tocopherol and N-acetylcysteine [182]. This combination previously in study conduced for Bagh [182] had been proved to decrease lipid peroxidation and protein carbonylation in the brain of old rats, in addition to enhancing the antioxidant defense by increasing the intracellular GSH content [82]. However, by not having tested the isolated supplements, there is no way to affirm which substance exercised greater beneficial effect, or whether some effect was suppressed or enhanced (antagonism or synergism).

4.4. LA Shows Neuroprotective Effects Mainly in Animal Models

In the past 5 years, only 4 studies evaluated the LA neuro-action in humans [71-74]. LA had been shown to have more intense neuroprotective effects in animal models preventing neurological damage characteristic of Parkinson's disease [130] and improvement in cognitive performance [131] and memory retention [126]. This may be due to the ability of LA to overcome the blood-brain barrier and to accumulate in the brain tissue, thereby exerting its antioxidant action [2]. Furthermore, it was suggested that LA, through its scavenging ability on reactive oxygen species (ROS), helps in the recycling of GSH, an endogenous antioxidant, essential for the control of cerebral redox imbalance [183], as well as in reducing levels of nitric oxide (·NO), molecule responsible for neuronal apoptosis [184].

In subjects with Alzheimer disease, Galasko [74] observed a reduction of OS in the brain, but Shinto [73] found a decrease in cognitive and functional measures. By studying multiple sclerosis, Khalili [71] detected the reduction of levels of some inflammatory markers. In schizophrenia, Vidović [72] detected an increase of advanced glycation end products (AGEs) and reduction of SOD activity in schizofrenics. These results prove the necessity of additional studies in this area.

4.5. LA Oral Supplementation Shows Protective and Therapeutic Effects Against Cancer in Animal Models

No study has been found that evaluated LA in prevention or in treatment in neoplasic processes in humans. However, the official site of the American Cancer Society in the internet, cites LA as a possible alternative supplement in cancer treatment, given positive experimental results, which includes improved survival [137] and reduction in unwanted effects of chemotherapy [94].

This LA action probably occurs because OS is intrinsically related to the development of cancer, including angiogenesis and production of pro-inflammatory cytokines (Interleukin 6, IL-6), transforming growth factor β - TGF-β -, Tumor necrosis factor-alpha - TNF-α -, among others) [185], besides generation of ROS by the tumor itself [186].

Nonetheless, the same Society puts aside concerns about its use, since the increase of ROS, through reduction of GSH and thioredoxin levels, is one of the targets of several anticancer drugs that act inducing the neoplastic cells, which presented rapid differentiation, to apoptosis. For this reason, the use of antioxidants during cancer treatment is still controversial in the scientific community [186,187]. However, even the antioxidants chemopreventive action has been questioned. In a recent review published by Potter [188], the author brings a lot of evidence that antioxidant agents conceptually known as chemopreventive, such as retinol, vitamin E, selenium, failed to show positive effects in several cohort studies.

Thus, the action of LA on the prevention and treatment should be evaluated further, before its general clinical recommendation.

4.6. LA is an Important Ally in Combating Inflammation and Pain

The benefits of using LA for pain and inflammatory diseases were clearly identified. Data on rheumatoid arthritis [59,140], chronic pain [60,69,70], neuropathy [62,65-67], migraines [189], ulcerative colitis [138] and splenic inflammatory response [139,190] were positive.

A meta-analysis published in 2004, after investigation of 4 randomized controlled clinical trials, admitting n=1258 diabetics, concluded that the use of LA (600 mg/day) for a short period of time (3 weeks) was superior to the placebo in the treatment of neuropathic and deficit symptoms in patients with diabetic neuropathy, confirming the significant effect of LA in combating pain [176]. A similar result was obtained

by the SYDNEY 2 trial, published in 2006 [176]. According to this trial, an oral supplementation of 600 mg/day of LA for 5 weeks was able to reduce the deficits and neuropathic symptoms in diabetic patients [177]. Note that this recommendation was based on comparative results between the initial results (pre-treatment) and final results (post-treatment) of the Total Symptom Score (TSC). It must be remembered that, in this multicenter model, a placebo group was used.

Among LA anti-inflammatory effects identified in animal models, there is a decrease in C-reactive protein (CRP) [101], IL-1β [59], TNF-α [140] and NF-kB [31], in the tissue concentrations of IL-6 [30,101,138], TNF-α [140] and IL- serum levels; in addition to decreased of expression of NF-kB [30], IL-6 [74 -75] and increased of expression of Nrf2 [97].

In vitro studies suggest that LA acts as an inhibitor of IκB kinase-2 (IKK2), an enzymatic complex responsible for degradation of the inhibitor-kappa B-α (IκBα) and subsequent NF-kB release [32]. Another anti-inflammatory effect assigned to LA is the elevation of Nrf2 intracellular levels that occurs through independent mechanisms of breaking link between Nrf2 and Keap 1 (Kelch ECH associating protein 1) (Fig. **2**) This fact led to increased expression of enzymatic antioxidant, such as GPx, SOD and others [191].

4.7. Controversial Effects of LA on Kidney Diseases

Subjects with chronic renal failure were investigated, in several studies [75,81]. LA treatment led to contradictory results. Some studies had shown no alteration in redox profile [78,81] or inflammation [77,81]. On the other hand, Showkat [76] identified a prejudicial effect of LA, by the increase of oxidative damage (increased of serum levels of MDA, F2-isoprostane and lipid hydroperoxides). However, improvement on markers normally not studied in the LA treatment, was observed in kidney diseases, such as adequacy on nutritional status, identified by subjective global assessment (SGA) [78], and a reduction of necessary erythropoietin dose to maintain hemoglobin levels normal [79]. According to Showkat [76], the negative effects of LA can be attributed to DHLA, able to also produce a pro-oxidant effect in the presence of transition metal cations, such as iron by reducing Fe^{3+} to Fe^{2+}, which can promote the generation of hydroxy radicals, through Fenton reaction.

4.8. LA: Antioxidant of the Future?

Due to controversial experimental observations (Tables **1** and **2**), LA continues to be a subject of intense interest in diseases where RONS are involved.

The redox pair LA/DHLA acts as a strong reducing agent and, under physiological conditions, only the $NAD(P)H/NAD(P)^+$ has a more negative reducing potential [192].

Furthermore, LA and DHLA are amphipathic molecules (depends on the environment and on the pH). They may act as antioxidants in hydrophilic and lipophilic [9] environments, making them effective in disabling RONS, such as the hydroxy radical ($OH^{\bullet}$), singlet oxygen ($^1O_2$), peroxynitrite ($ONOO^-$), and $^{\bullet}NO$ [184,193]. As such, the redox couple prevents lipid peroxidation of the cell membranes, inhibits the formation of cyclooxygenase-1 (COX-1) and act as a chelating agent of transition metal ions [86] (Fig. **1**).

Moreover, LA also acts as a mediator of cell signaling, inducing the *de novo* synthesis of GSH transcriptionally [2], by stimulating increased levels of Nrf2, the most important transcription factor that regulates genes that contain the antioxidant response element [191].

Another LA action is to restore enzymatic and non-enzymatic antioxidant systems, such as GSH, ascorbate, α - tocopherol, catalase and glutathione peroxidase (GPx) [194]. However, the *in vivo* balance between anti- and pro-oxidant effects of LA still remains uncertain and controversial [181].

LA anti-inflammatory effects (Fig. **2**) are intrinsically related to its antioxidant activity (Fig. **1**). It is known that ROS increase pro-inflammatory cytokines and the synthesis of chemotactic molecules which promote vagus nerve inflammatory process, and consequently lead to pain [60]. Ischemia, one of the mechanisms involved in neuropathic pain, also increases production of ROS and reduces oxygen and nutrients supply to nerve cells, resulting in necrosis of these cells [195].

Furthermore, several studies confirm that LA inhibits the activation of NF-kB [25,138], a ROS-activated transcription factor with pro-inflammatory activity. NF-kB is involved in the expression of several pro-inflammatory cytokines such as IL-4, IL-5, TNF-α [25], soluble receptor activator of NF-kB (sRANKL) [100], chemokines and intercellular adhesion molecules [196].

All these actions justify the growing scientific interest in LA.

Besides the pathologies and clinical conditions discussed above, the present review also identified several clinical disorders in which LA was successfully tested, such as kidney disorders [80,159], genetic and hereditary diseases [91,197], intoxication [152,153], among others [31,154], indicating the large field of action of LA, which may explain its characterization as an antioxidant for the future [42].

4.9. Critical Analysis and Possible Directions

Given the diversity of clinical and pathological situations in which LA was tested both in animal models and in humans, the results, many times, appear conflicting.

One of the possible factors contributing to this is the diversity of biological markers (Fig. **3**) used in the analysis.

In human studies, in addition to classical serum markers (lipid and glucose profile), some others were tested, such as inflammatory parameters (TNF-α, IL-6 and IL-1β) and redox imbalance biomarkers [total antioxidant capacity - TAC, SOD, carbonylated proteins, antioxidant enzymes (catalase, SOD) malondialdehyde, thiobarbituric acid reactive substances - TBARS, total thiols and GSH/GSSG). However, only a few markers showed to be sensitive to the action of LA, such as postprandial glycemia, glycosylated hemoglobin (HbA1c) [55], SOD [86], TAC [89,91], GSH [91] and TBARS [55,91]. Even with the use of these markers, there is no universal agreement among the authors, for instance

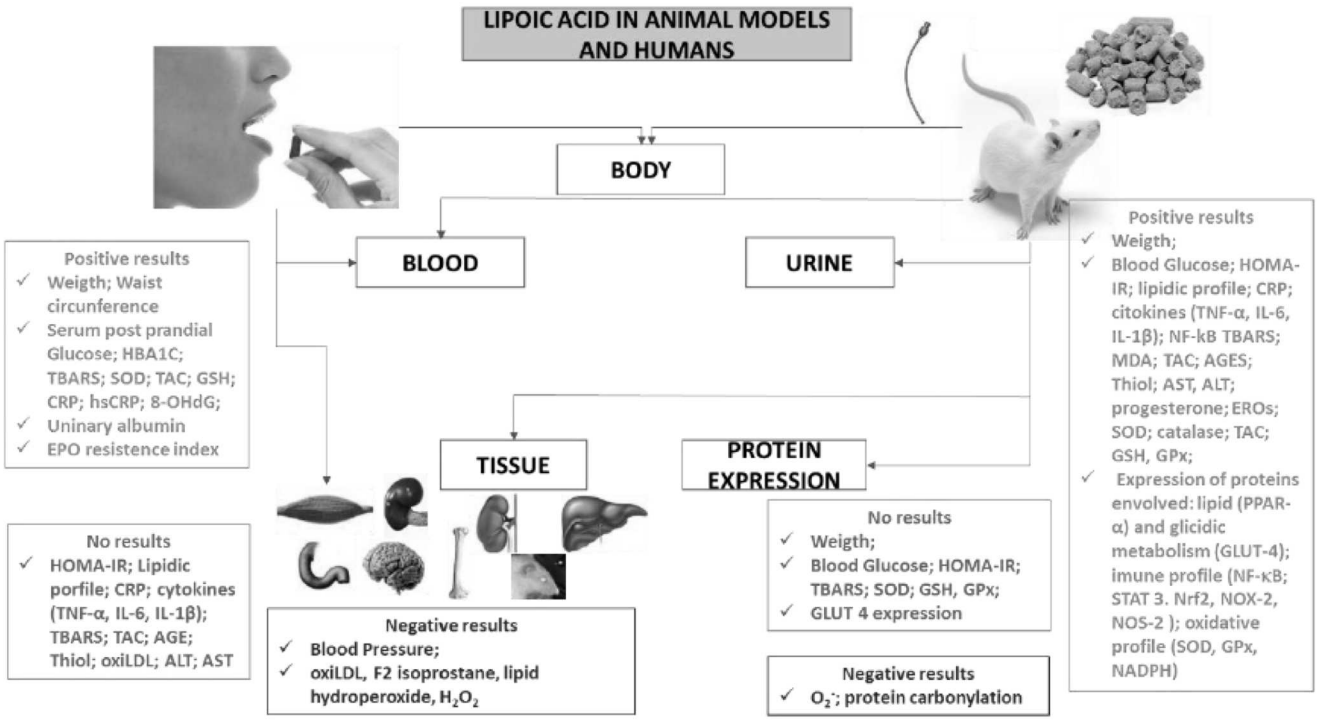

Fig. (3). Main markers used for evaluation of the antioxidant and anti-inflammatory profile of LA (tissue, blood and urine).

Legend: 8OHdG = 8-hydroxy-2-deoxyguanosine; AGE = advanced glycation end products; ALT - alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; EPO = erythropoietin; GSH = reduced glutathione; GPx = glutathione peroxidase; GLUT4 = Glucose transporter type 4; HbA1c = glycosylated hemoglobin; HOMA - IR = the insulin/fasting glucose to assess insulin resistance; hsCRP = highly sensitive C-reactive protein; NADPH = Nicotinamide adenine dinucleotide phosphate reduced; NF-kB = (nuclear factor kappa-light-chain-enhancer of activated B cells); Nrf2 = nuclear erythroid 2-related factor 2; NOS-2 = Nitric oxide synthase 2; NOX-2 = nicotinamide adenine dinucleotide phosphate oxidase 2; $O_2^{\cdot-}$ = superoxide radical anion; oxiLDL = oxidized low density lipoprotein; SOD = superoxide dismutase; TAC = total antioxidant capacity; TBARS = thiobarbituric acid reactive substances; TNF-α = tumor necrosis factor alpha.

malondialdehyde (MDA) and F2-isoprostane, markers of lipid peroxidation, like TBARS had not shown effects after supplementation with LA [80,81].

As shown in Tables **1** and **2**, the positive results of LA are observed in several randomized studies [59,60,62], double-blinded [59,66,67]. However, only two studies used a placebo [59,66], and demonstrated LA beneficial effects.

On the other hand, in animal models, there is a diversity of markers, both in serum (lipid profile, glucose, redox, etc.) as well as in tissues (redox activity - SOD, catalase, glutathione peroxidase - GPx -, MDA, carbonylated proteins, AGEs, 4-Hydroxynonenal - 4-HNE, among others - inflammatory - TNF-α, IL-1β, IL-6, etc) or gene expression markers (proteins involved in pro or anti-inflammatory activity, glucose and lipid metabolism, etc), in addition to mitochondrial redox markers (8-OHdG, mitochondrial membrane potential, NADPH activity). However, and probably due to this, diversity and also the specific characteristics of each tissue analyzed, biomarkers do not always show sensitivity to the LA action. It can be exemplified by the variation in SOD results, which had increased levels in blood [139,152,154], in the liver [101], in skeletal muscle [110,111], in kidney [113], in spleen [139], in duodenum [154], in brain [152], in the sciatic nerve [108], in testicles [146] and in the bone [155], but not in the cornea [149], after LA supplementation.

From this diversified data, it is urgent the identification of sensitive biomarkers (serum/urine/tissue) that respond to the action of LA and can be used in various clinical and/or pathological situations. Then, their use can be standardized in these situations and might finally lead to conclusion about the LA supplementation being beneficial or not.

Another complicating factor in the analysis of the data presented in this review was the fact that 50% of the studies for humans, used LA along with antioxidant vitamins or not [47,49,50,54,81,93], with substances with antioxidant effects [58-60,62,65,69,70] or physiotherapy [60]. As previously discussed, the use of combinatorial therapy made it difficult to discriminate the specific role of each component, raising difficulties to attribute beneficial, synergistic or antagonistic effects. This fact may be one reason for the low effectiveness of LA in humans, since in animal studies, the vast majority (77.5%) use isolated administration of LA.

Despite this beneficial properties of LA/DHLA, it is critical to conduct additional experiments in humans and to establish effective doses and length of treatment for each clinical situation studied, along with a definite proof of antagonism and synergism effects in cases where combinatorial approaches are used. Biomarkers have to be best defined and standardized, in terms of protocols, unities, etc., to allow comparison between the findings, *in vitro* and in clinical studies.

In the future, to minimize these drawbacks, it would be necessary to use new biological testing models or mathematical/statistical methods to distinguish among several parameters.

CONCLUSION

The use of LA is of undeniable interest in several areas of health. However, many questions need still to be answered. Is this acid, beyond its physiological value, an effective supplement for humans, as was seen in animal models? Has it the capacity to reduce oxidative and/or inflammatory activity? Does it have hematological and/or hormonal actions?

Although most studies focus on obesity and cardiometabolic diseases, the positive results of LA in humans can be questioned, in virtue of few positive results, unlike those found in animal models, indicating a possible variation between species, or lack of standardization of dose and duration of supplementation.

The effects of LA on aging process and neurological disorders in humans should be more fully evaluated since experimental tests seem to demonstrate various beneficial effects like preventing damage to neurons, characteristic of different neurological diseases and the natural process of aging itself.

The action of LA in both prevention as well as treatment of cancer should be better evaluated at the experimental level, as well as *in vitro* studies, before further testing in humans. The role of redox imbalance in the induction of the neoplasic process and in the chemotherapy treatment is still ground for important discussions in the scientific community.

One area that continues to show promising results for the use of LA is chronic pain associated with an underlying disease, as peripheral neuropathy, or migraines. All the studies evaluated were unanimous to report that LA alone or combined with various substances, was able to improve the complaints of pain and in some cases, even the conduction of nerve impulses, confirming the anti-inflammatory and antioxidant effects of LA.

Therefore, new meta-analyses are needed to better guide health professionals regarding the safety of prescribing LA as a supplement.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

AUTHORS' CONTRIBUTION

MSc Fabiana Andréa Moura designed the study, reviewed the literature, wrote the first draft and prepared the schemes. Kivia Queiroz de Andrade reviewed the literature and wrote the first draft. Dr. Juliana Célia de Farias Santos reviewed the first draft. Prof. Marília Oliveira Fonseca Goulart critically reviewed the paper and supervised the work.

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Received: ????????????????? Revised: ????????????????? Accepted: ?????????????????

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