

# α-Lipoic Acid

Subjects: Biology

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α-lipoic acid (ALA, thioctic acid) is an organosulfur component produced from plants, animals, and humans. It has various properties, among them great antioxidant potential and is widely used as a racemic drug for diabetic polyneuropathy-associated pain and paresthesia. Naturally, ALA is located in mitochondria, where it is used as a cofactor for pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase complexes. Despite its various potentials, ALA therapeutic efficacy is relatively low due to its pharmacokinetic profile. Data suggests that ALA has a short half-life and bioavailability (about 30%) triggered by its hepatic degradation, reduced solubility as well as instability in the stomach. However, the use of various innovative formulations has greatly improved ALA bioavailability. The R enantiomer of ALA shows better pharmacokinetic parameters, including increased bioavailability as compared to its S enantiomer. Indeed, the use of amphiphilic matrices has capability to improve ALA bioavailability and intestinal absorption.

Keywords: α-lipoic acid ; bioavailability ; formulations ; clinical trial ; diabetic neuropathy ; obesity ; schizophrenia ; sclerosis ; pregnancy

## 1. Introduction

α-lipoic acid (ALA), also known as 1,2-dithiolane-3-pentanoic acid or thioctic acid, is a compound commonly found in mitochondria, necessary for different enzymatic functions. ALA was isolated by Reed in 1951 <sup>[1]</sup> as an acetate replacing factor and its first clinical use dates from 1959 in the treatment of acute poisoning by *Amanita phalloides*, also known death cap (from mushrooms) <sup>[2]</sup>.

Briefly, ALA is an organosulfur compound produced from plants, animals, and humans and exists in nature. In the Krebs cycle, ALA plays important roles in various chemical reactions, acting as a cofactor for some enzymatic complexes involved in energy generation for the cell. It also forms covalent bonds with proteins and has therapeutic potential. It has a single chiral center and asymmetric carbon which results in two optical isomers: R- and S- lipoic acid (**Figure 1**) <sup>[3]</sup>. Thus, ALA has two enantiomeric forms, called S and R enantiomers, considered mirror images of each other. Both S and R enantiomers are present equally in ALA, being however the R isomeric form present naturally, while the S isomer is prepared through chemical processes. Foods are a natural source of the R enantiomer, naturally produced inside the living organisms forming covalent bonds with proteins. While ALA exists in nature as R enantiomer, synthetic supplementation consists of a racemic composition of R and S forms <sup>[4]</sup>. Although synthesized by the human body at low amount, the ALA quantities produced are not enough to fulfill the energy requirement of the cell. Thus, it is mostly obtained from diet, especially from meat and vegetables. Fruits are also a source of this acid <sup>[5]</sup>.



**Figure 1.** The chemical structure of optical isomers of ALA.

On the other hand, ALA has numerous clinically valuable properties <sup>[5][6]</sup>. It acts as an enzymatic cofactor <sup>[7]</sup> and is also involved in glucose <sup>[8][9]</sup> and lipid <sup>[10]</sup> metabolism and manages gene transcription. ALA also acts as antioxidant because it not only improves but also restores the intrinsic antioxidant systems, and supports their production or cell accessibility <sup>[11][12][13]</sup>. It also efficiently removes heavy metals from blood stream, responsible for oxidative stress <sup>[11][13][14]</sup>. The most unique characteristic of ALA over other antioxidant substances is that it reacts as both lipid and water soluble compound <sup>[5][6]</sup>. There is no doubt that it is a strong antioxidant, but due to certain reasons its use for medicinal purposes is prohibited; however, in some states it is used as a supplement and in others as a remedy <sup>[5][6][15]</sup>. These restrictions are

due to some endogenous characteristics of substance by itself, such as the changeableness due to the disclosing of dithiolane ring and the emergence of disulfide bond between molecules. Other properties that limit the oral use of ALA are its decreased ability to become dissolved in the gastrointestinal tract and increased rate of hepatic metabolism. In addition, besides it is widely known antioxidant potential, ALA has also many other functions, as it is its involvement in mitochondria producing energy, by acting as cofactor for various enzymes involved in metabolism [5].

Moreover, ALA plays a vital role in glucose humiliation during metabolism. For instance, ALA has been applied as a racemic medication for diabetic polyneuropathy-associated pain and paresthesia [16]. ALA has also an important function in energy transduction through mitochondria [6][17]. Two reduced or oxidized thiol groups are present in the small molecule of ALA. The oxidized form is known as ALA or simply as lipoic acid, while the reduced form is noted as dihydrolipoic acid (DHLA). ALA inactivates free radicals and the reduced form also interacts with reactive oxygen species (ROS) [8]. Naturally, ALA is found in mitochondria where it binds to the E2 subunit and is used as a cofactor for both pyruvate dehydrogenase (PDH) and  $\alpha$ -ketoglutarate dehydrogenase complexes [18]. ALA is synthesized *de novo* at very small amounts in the body from cysteine and fatty acids, because of which there is a need to supplement it from exogenous sources [19].

ALA improves the glycemic control [6], alleviates diabetes mellitus (DM) complications [20][21] and even symptoms of peripheral neuropathy, at same time that effectively lessens the heavy metals toxicity [22].

## **2. $\alpha$ -Lipoic Acid Pharmacological Activities: An Overview**

Over the years, ALA has gained a considerable attention as a food additive with beneficial effects both in the treatment or management of several ailments [11][23][24]. ALA's pharmacological effects are primarily related with its antioxidant activity, but ALA and DHLA have also demonstrated interesting cardiovascular, cognitive, anti-ageing, detoxifying, anti-inflammatory, anti-cancer, and neuroprotective properties [24].

### **2.1. $\alpha$ -Lipoic Acid Antioxidant Potential**

There are vast literature data on ALA and DHLA antioxidant effects, namely acting as metal chelating agents, free radical scavengers, regenerator of endogenous antioxidants, such as glutathione, vitamins C and E and repair of oxidized damage [25]. The existence of thiol groups in ALA is responsible for its metal chelating abilities [14][24]. Moreover, it is able to increase the glutathione levels inside the cells, that chelate and excrete a wide variety of toxins, especially toxic metals from the body [24]. For instance, the study of Goralska et al. [26] showed that ALA administration led to a decrease in iron ions in epithelial cells. This change was associated with elevated cell resistance to hydrogen peroxide challenge, meaning that ALA exerts a direct impact in oxidative stress reduction [26]. Briefly, ALA is conceived as a biological antioxidant that is both water- and fat-soluble and is capable to neutralize ROS everywhere in the body, inside and outside the cells, and for this reason, ALA is being referred as the universal antioxidant [27][28][29].

### **2.2. $\alpha$ -Lipoic Acid Antidiabetic Potential**

Among the metabolic disorders, diabetes mellitus (DM) represent a serious health problem, currently affecting approximately 422-million people worldwide [30]. It is designated by disturbances on carbohydrates, lipids, and proteins metabolism [31]. Also, it has been recognized as a major risk factor for the development of several human diseases, including atherosclerosis, hypertension, heart failure, myocardial infarction, neuropathic pain and even stroke [32]. Emerging evidences demonstrate that DM results from the excessive ROS generation and impairment of the antioxidant potential [33][34][35]. Several studies have highlighted the potential use of ALA in diabetes, due to its ability to increasing both sugar uptake in insulin-sensitive and insulin-resistant muscle tissues [4][36], and to stimulate the glucose uptake by the repartition of glucose transporters to the plasma membrane, and tyrosine phosphorylation of insulin receptor substrate-1 [9].

### **2.3. $\alpha$ -Lipoic Acid and Alzheimer's Disease**

Alzheimer's disease (AD) is a neurological disease characterized by cognitive, functional, and behavioral alterations. Memory loss has been linked to the formation of beta-amyloid plaques and the uprise of tau in a pathological form in patients with AD [37][38]. Substantial evidences have supported the implication of oxidative stress in the pathogenesis of AD [39][40][41]. Non-steroidal anti-inflammatory drugs (NSAIDs) have been proposed for the therapy of neurodegenerative diseases, including AD. However, the prolonged NSAIDs administration results in gastrointestinal toxicity due cyclooxygenase (COX) inhibition [24][42]. To overcome this limitation, ALA has been selected based on the intended role of oxidative stress in the development of AD.

In vitro investigations have indicated that ALA has neuroprotective effects on A $\beta$ -mediated cytotoxicity [43][44][45], namely through defending cortical neurons from cytotoxicity induced by A $\beta$  or H<sub>2</sub>O<sub>2</sub> [46], partially attributed to the activation of PKB/Akt signaling pathway. Another study revealed that ALA has ability to effectively protect cultured hippocampal neurons against both A $\beta$  peptide and Fe/H<sub>2</sub>O<sub>2</sub> mediated toxicity [47].

Studies have also shown that ALA show anti-dementia or anti-AD properties by increasing acetylcholine (ACh) production through activation of choline acetyltransferase, which increases glucose absorption and, hence, supply more acetyl-CoA for ACh production [48]. Haugaard and Levin (2000) reported that DHLA significantly increased the activity of a purified preparation of choline acetyltransferase, and that its removal by dialysis from a partially purified of choline acetyltransferase led to a complete disappearance of enzyme activity and that its addition restores activity towards normal levels. The same finding was obtained when the experiments were repeated with extracts of rat brain and heart as well as rabbit bladder tissue. Thus, the authors concluded that it may act as a coenzyme in the choline acetyltransferase reaction [49].

On the other hand, inflammation has a key function in AD. It is engaged around amyloid plaques, surrounded by activated astrocytes and microglia, and is characterized by elevated levels of free radicals and pro-inflammatory cytokines [50], with TNF- $\alpha$  being considered an indicator from mild cognitive impairment to AD [48][51]. ALA has multiple and complex effects in this way, namely scavenging ROS, transition metal ions, increasing the levels of reduced glutathione [48][52], scavenging of lipid peroxidation products [51][53][54] and even acting on signal transduction pathways [52][55]. Similarly, Dinicola et al. [56] found that ALA downregulated the levels of the inflammatory cytokines IL-1B and IL-6 in SK-N-BE human neuroblastoma cells through DNA methylation-dependent modulation, paving the way for the impact of epigenetic mechanisms in AD control/prevention.

## 2.4. $\alpha$ -Lipoic Acid and Cancer

An increasing body of literature highlight on the potential application of ALA in cancer therapy [57][58]. Cancer cells convert glucose preferentially to lactate for ATP generation, a phenomenon known as the Warburg effect or aerobic glycolysis. The persistent activation of aerobic glycolysis in cancerous cells lead to oncogenes activation or loss of tumor suppressors, thereby causing cancer progression. In this respect, the inhibition of aerobic cycle may contribute to anticancer effects [59][60]. Pyruvate dehydrogenase catalyzes pyruvate to acetyl CoA conversion, thus preventing lactate production. Feurecker et al. investigated whether ALA is capable of activating pyruvate dehydrogenase in tumor cells. The results show that ALA inhibited cell proliferation, [18F]-FDG uptake and lactate formation and increased apoptosis in neuroblastoma cell lines Kelly, SK-N-SH, Neuro-2a and in the breast cancer cell line SkBr3. In the mouse xenograft model with subcutaneously SkBr3 cells, daily treatment with ALA has delayed tumor growth [61].

ALA suppressed thyroid cancer cell proliferation and growth through activation of AMPK and subsequent down-regulation of mTOR-S6 signaling pathway in BCPAP, HTH-83, CAL-62 and FTC-133 cells lines. In the same study, it was also found that ALA also significantly inhibited tumor growth in mouse xenograft model using BCPAP and FTC-133 cells [62]. In lung cancer cells, ALA inhibited cell proliferation through Grb2-mediated EGFR down-regulation [63].

Studies have also shown that ALA is able to generate ROS, which promote ALA-dependent cell death in lung cancer [64], breast cancer [65] and colon cancer [66][67], suggesting that it triggers the mitochondrial pathway of apoptosis in cancer cells. Recently, the effects of ALA on the migration and invasion of breast cancer cells were assessed [68]. The results have showed that ALA inhibited metastatic breast cancer cells migration and invasion, partly through ERK1/2 and AKT signaling. In summary, the scientific data show that ALA could be applied for cancer management and prevention.

# 3. Preclinical Actability of $\alpha$ -Lipoic Acid

## 3.1. Anti-diabetic Properties of $\alpha$ -Lipoic Acid

As previously noted, ALA have shown to be useful for increasing sugar uptake in insulin-sensitive and insulin-resistant muscle tissues [4][36]. In addition, the triglycerides' storage in the body led to type-2 DM progression. When activated, AMP-activated protein kinase (AMPK) increase sugar uptake, fatty acids oxidation and mitochondrial biogenesis. In obese rats, muscle AMPK levels are reduced. However, when these rats were submitted to ALA administration, a raise in insulin-stimulated glucose disposal in skeletal muscle and in the whole body was observed. ALA was also found to increase lipid oxidation and activated AMPK. These results suggest that ALA ameliorate insulin sensitivity through AMPK activation [69]. Konrad et al. [9] have demonstrated that ALA stimulates glucose uptake by the repartition of glucose transporters to the plasma membrane, and tyrosine phosphorylation of insulin receptor substrate-1. In a study carried out by Bitar et al. [70] it was found that the intake of 50 mg/kg for 30 days averted diabetes-mediated mitochondrial and endothelial dysfunction in

rats, via a signal transduction pathway. It is known that in DM, the NO bioavailability is reduced through modulation of the endothelial nitric oxide synthase (eNOS) activity and oxidative stress [71]. In endothelial cells of aged rats, ALA intake resulted in a decrease in eNOS phosphorylation through Akt [72]. ALA is able to trigger Akt phosphorylation in human umbilical vascular endothelial cells and in THP-1 human monocyte cell lines [73][74]. These findings propose that the improved endothelial function due to ALA is partially ascribed to eNOS recoupling and increased NO bioavailability [74]. Thus, the use of ALA as an adjuvant in DM management is related to its capability to inhibit glycation which generates free radicals [74][75][76]. Overall, the information amassed herein indicated the potential therapeutic value of ALA for the treatment of DM.

### 3.2. $\alpha$ -Lipoic Acid and Alzheimer's Disease

Given the above highlighted aspects on the use of ALA for neurodegenerative conditions, specifically in AD, Quinn et al. [77] assessed the effect of a diet supplemented with ALA on hippocampus-dependent memory of aged Tg2576 mice with AD. The authors found that ALA led to a marked improvement in learning and memory retention [77], and no significant differences were found in  $\beta$ -amyloid levels between ALA-treated and untreated Tg2576 mice [78].

### 3.3. $\alpha$ -Lipoic Acid and Pregnancy

Considering the promising antioxidant potential of ALA and its impact in multiple inflammatory conditions, recent evidences have increasingly highlighted its impact in physiological processes, such as pregnancy. Interestingly, Micili et al. [79] assessed the impact of ALA vaginal administration in female Wistar rats, namely testing its tissue distribution, impact on implantation process and effectiveness in contrasting induced preterm birth. Curiously, the authors found that vaginal ALA is well-absorbed and distributed, without affecting the implantation process and was even able to significantly revert mifepristone plus prostaglandin E2 effects, thus, delaying the delivery timing and decreasing the synthesis of mRNA and pro-inflammatory cytokines release [79].

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## References

1. Reed, L.J.; DeBusk, B.G.; Gunsalus, I.C.; Hornberger, C.S. Crystalline  $\alpha$ -lipoic acid: A catalytic agent associated with pyruvate dehydrogenase. *Science* 1951, 114, 93–94.
2. Bock, E.; Schneeweiss, J. Ein Beitrag zur Therapie der Neuropathia diabetica. *Munch. Med. Wochenschr.* 1959, 43, 1911–1912.
3. Brookes, M.H.; Golding, B.T.; Howes, D.A.; Hudson, A.T. Proof that the absolute configuration of natural  $\alpha$ -lipoic acid is R by the synthesis of its enantiomer [(S)-(–)- $\alpha$ -lipoic acid] from (S)-malic acid. *J. Chem. Soc. Chem. Commun.* 1983, 19, 1051–1053.
4. Ghibu, S.; Richard, C.; Vergely, C.; Zeller, M.; Cottin, Y.; Rochette, L. Antioxidant properties of an endogenous thiol: Alpha-lipoic acid, useful in the prevention of cardiovascular diseases. *J. Cardiovasc. Pharmacol.* 2009, 54, 391–398.
5. Brufani, M. Acido  $\alpha$ -lipoico farmaco o integratore. Una panoramica sulla farmacocinetica, le formulazioni disponibili e le evidenze cliniche nelle complicanze del diabete. *Prog. Nutr.* 2014, 16, 62–74.
6. Singh, U.; Jialal, I. Retracted: Alpha-lipoic acid supplementation and diabetes. *Nutr. Rev.* 2008, 66, 646–657.
7. Maglione, E.; Marrese, C.; Migliaro, E.; Marcuccio, F.; Panico, C.; Salvati, C.; Citro, G.; Quercio, M.; Roncagliolo, F.; Torello, C.; et al. Increasing bioavailability of (R)-alpha-lipoic acid to boost antioxidant activity in the treatment of neuropathic pain. *Acta Bio-Medica Atenei Parm.* 2015, 86, 226–233.
8. Packer, L.; Cadenas, E. Lipoic acid: Energy metabolism and redox regulation of transcription and cell signaling. *J. Clin. Biochem. Nutr.* 2010, 48, 26–32.
9. Konrad, D.; Somwar, R.; Sweeney, G.; Yaworsky, K.; Hayashi, M.; Ramlal, T.; Klip, A. The antihyperglycemic drug alpha-lipoic acid stimulates glucose uptake via both GLUT4 translocation and GLUT4 activation: Potential role of p38 mitogen-activated protein kinase in GLUT4 activation. *Diabetes* 2001, 50, 1464–1471.
10. Chen, W.-L.; Kang, C.-H.; Wang, S.-G.; Lee, H.-M.  $\alpha$ -Lipoic acid regulates lipid metabolism through induction of sirtuin 1 (SIRT1) and activation of AMP-activated protein kinase. *Diabetologia* 2012, 55, 1824–1835.
11. Gorąca, A.; Huk-Kolega, H.; Piechota, A.; Kleniewska, P.; Ciejk, E.; Skibska, B. Lipoic acid—biological activity and therapeutic potential. *Pharmacol. Rep.* 2011, 63, 849–858.
12. Han, D.; Handelman, G.; Marcocci, L.; Sen, C.K.; Roy, S.; Kobuchi, H.; Tritschler, H.J.; Flohé, L.; Packer, L. Lipoic acid increases de novo synthesis of cellular glutathione by improving cystine utilization. *Biofactors* 1997, 6, 321–338.

13. Shay, K.P.; Moreau, R.F.; Smith, E.J.; Smith, A.R.; Hagen, T.M. Alpha-lipoic acid as a dietary supplement: Molecular mechanisms and therapeutic potential. *Biochim. Biophys. Acta* 2009, 1790, 1149–1160.
14. Ou, P.; Tritschler, H.J.; Wolff, S.P. Thioctic (lipoic) acid: A therapeutic metal-chelating antioxidant? *Biochem. Pharmacol.* 1995, 50, 123–126.
15. Bilska, A.; Wlodek, L. Lipoic acid-the drug of the future. *Pharmacol. Rep.* 2005, 57, 570–577.
16. Castro, M.C.; Villagarcía, H.G.; Massa, M.L.; Francini, F. Alpha-lipoic acid and its protective role in fructose induced endocrine-metabolic disturbances. *Food Funct.* 2019, 10, 16–25.
17. Keith, D.J.; Butler, J.A.; Berner, B.; Dixon, B.; Johnson, S.; Garrard, M.; Sudakin, D.L.; Christensen, J.M.; Pereira, C.; Hagen, T.M. Age and gender dependent bioavailability of R- and R,S-alpha-lipoic acid: A pilot study. *Pharmacol. Res.* 2012, 66, 199–206.
18. Packer, L.; Witt, E.H.; Tritschler, H.J. alpha-Lipoic acid as a biological antioxidant. *Free Radic. Boil. Med.* 1995, 19, 227–250.
19. Carreau, J.-P. [32] Biosynthesis of lipoic acid via unsaturated fatty acids. *Meth. Enzymol.* 1979, 62, 152–158.
20. Ziegler, D. Thioctic acid for patients with symptomatic diabetic polyneuropathy: A critical review. *Treat Endocrinol* 2004, 3, 173–179.
21. Henriksen, E.J. Exercise training and the antioxidant alpha-lipoic acid in the treatment of insulin resistance and type 2 diabetes. *Free Radic. Boil. Med.* 2006, 40, 3–12.
22. Ciftci, H.; Bakal, U. The effect of lipoic acid on macro and trace metal levels in living tissues exposed to oxidative stress. *Anti-Cancer Agents Med. Chem.* 2009, 9, 560–568.
23. Park, S.; Karunakaran, U.; Jeoung, N.H.; Jeon, J.-H.; Lee, I.-K. Physiological effect and therapeutic application of alpha lipoic acid. *Curr. Med. Chem.* 2014, 21, 3636–3645.
24. El Barky, A.R.; Hussein, S.A.; Mohamed, T.M. The potent antioxidant alpha lipoic acid. *J. Plant Chem. Ecophysiol.* 2017, 2, 1016.
25. Biewenga, G.P.; Haenen, G.R.; Bast, A. The pharmacology of the antioxidant lipoic acid. *Gen. Pharmacol. Vasc. Syst.* 1997, 29, 315–331.
26. Goralska, M.; Dackor, R.; Holley, B.; McGahan, M.C. Alpha lipoic acid changes iron uptake and storage in lens epithelial cells. *Exp. Eye Res.* 2003, 76, 241–248.
27. Suzuki, Y.J.; Tsuchiya, M.; Packer, L. Thioctic acid and dihydrolipoic acid are novel antioxidants which interact with reactive oxygen species. *Free Radic. Res. Commun.* 1991, 15, 255–263.
28. Scott, B.C.; Aruoma, O.I.; Evans, P.J.; O'Neill, C.; Van der Vliet, A.; Cross, C.E.; Tritschler, H.; Halliwell, B. Lipoic and dihydrolipoic acids as antioxidants. A critical evaluation. *Free Radic. Res.* 1994, 20, 119–133.
29. Islam, M.T. Antioxidant activities of dithiol alpha-lipoic acid. *Bangladesh J. Med. Sci.* 2009, 8, 34–49.
30. WHO. Diabetes; World Health Organization: Geneva, Switzerland, 2018.
31. Moodley, K.; Joseph, K.; Naidoo, Y.; Islam, S.; Mackraj, I. Antioxidant, antidiabetic and hypolipidemic effects of *Tulbaghia violacea* Harv. (wild garlic) rhizome methanolic extract in a diabetic rat model. *BMC Complement. Altern. Med.* 2015, 15, 408.
32. Beckman, J.A.; Creager, M.A.; Libby, P. Diabetes and atherosclerosis: Epidemiology, pathophysiology, and management. *J. Am. Med. Assoc.* 2002, 287, 2570–2581.
33. Giacco, F.; Brownlee, M. Oxidative stress and diabetic complications. *Circ. Res.* 2010, 107, 1058–1070.
34. Pitocco, D.; Tesaro, M.; Alessandro, R.; Ghirlanda, G.; Cardillo, C. Oxidative Stress in Diabetes: Implications for Vascular and Other Complications. *Int. J. Mol. Sci.* 2013, 14, 21525–21550.
35. Asmat, U.; Abad, K.; Ismail, K. Diabetes mellitus and oxidative stress-A concise review. *Saudi Pharm. J.* 2016, 24, 547–553.
36. Eason, R.C.; Archer, H.E.; Akhtar, S.; Bailey, C.J. Lipoic acid increases glucose uptake by skeletal muscles of obese diabetic ob/ob mice. *Diabetes Obes. Metab.* 2002, 4, 29–35.
37. García-Osta, A.; Cuadrado-Tejedor, M.; García-Barroso, C.; Oyarzábal, J.; Franco, R. Phosphodiesterases as therapeutic targets for Alzheimer's disease. *ACS Chem. Neurosci.* 2012, 3, 832–844.
38. Wu, Y.; Li, Z.; Huang, Y.Y.; Wu, D.; Luo, H.B. Novel phosphodiesterase inhibitors for cognitive improvement in Alzheimer's disease. *J. Med. Chem.* 2018, 61, 5467–5483.
39. Perry, G.; Cash, A.D.; Smith, M.A. Alzheimer disease and oxidative stress. *J. Biomed. Biotechnol.* 2002, 2, 120–123.

40. Chen, Z.; Zhong, C. Oxidative stress in Alzheimer's disease. *Neurosci. Bull.* 2014, 30, 271–281.
41. Huang, W.-J.; Zhang, X.; Chen, W.-W. Role of oxidative stress in Alzheimer's disease. *Biomed. Rep.* 2016, 4, 519–522.
42. Cacciatore, I.; Marinelli, L.; Fornasari, E.; Cerasa, L.S.; Eusepi, P.; Türkez, H.; Pomilio, C.; Reale, M.; D'Angelo, C.; Costantini, E.; et al. Novel NSAID-derived drugs for the potential treatment of Alzheimer's disease. *Int. J. Mol. Sci.* 2016, 17, 1035.
43. Hagen, T.M.; Ingersoll, R.T.; Lykkesfeldt, J.; Liu, J.; Wehr, C.M.; Vinarsky, V.; Bartholomew, J.C.; Ames, A.B. (R)-alpha-lipoic acid-supplemented old rats have improved mitochondrial function, decreased oxidative damage, and increased metabolic rate. *FASEB J.* 1999, 13, 411–418.
44. Farr, S.A.; Poon, H.F.; Dogrukol-Ak, D.; Drake, J.; Banks, W.A.; Eyerman, E.; Allan Butterfield, D.; Morley, J.E. The antioxidants alpha-lipoic acid and N-acetylcysteine reverse memory impairment and brain oxidative stress in aged SAMP8 mice. *J. Neurochem.* 2003, 84, 1173–1183.
45. Ono, K.; Hirohata, M.; Yamada, M.  $\alpha$ -Lipoic acid exhibits anti-amyloidogenicity for  $\beta$ -amyloid fibrils in vitro. *Biochem. Biophys. Res. Commun.* 2006, 341, 1046–1052.
46. Zhang, W.-J.; Frei, B. Alpha-lipoic acid inhibits TNF-alpha-induced NF-kappaB activation and adhesion molecule expression in human aortic endothelial cells. *FASEB J.* 2001, 15, 2423–2432.
47. Lovell, M.A.; Xie, C.; Xiong, S.; Markesbery, W. Protection against amyloid beta peptide and iron/hydrogen peroxide toxicity by alpha lipoic acid. *J. Alzheimer's Dis.* 2003, 5, 229–239.
48. Holmquist, L.; Stauchbury, G.; Berbaum, K.; Muscat, S.; Young, S.; Hager, K.; Engel, J.; Münch, G. Lipoic acid as a novel treatment for Alzheimer's disease and related dementias. *Pharmacol. Ther.* 2007, 113, 154–164.
49. Haugaard, N.; Levin, R.M. Regulation of the activity of choline acetyl transferase by lipoic acid. *Mol. Cell. Biochem.* 2000, 213, 61–63.
50. Meraz-Ríos, M.A.; Toral-Rios, D.; Franco-Bocanegra, D.; Villeda-Hernández, J.; Campos-Peña, V. Inflammatory process in Alzheimer's disease. *Front. Integr. Neurosci.* 2013, 7, 59.
51. Ooi, L.; Patel, M.; Münch, G. The thiol antioxidant lipoic acid and Alzheimer's disease. In *Systems Biology of Free Radicals and Antioxidants*; Laher, I., Ed.; Springer: Berlin/Heidelberg, Germany, 2014; pp. 2275–2288.
52. Suh, J.H.; Wang, H.; Liu, R.-M.; Liu, J.K.; Hager, T.M. (R)- $\alpha$ -Lipoic acid reverses the age-related loss in GSH redox status in post-mitotic tissues: Evidence for increased cysteine requirement for zGSH synthesis. *Arch. Biochem. Biophys.* 2015, 423, 126–135.
53. Hardas, S.S.; Sultana, R.; Clark, A.M.; Beckett, T.L.; Szveda, L.I.; Murphy, P.; Butterfield, D.A. Oxidative modification of lipoic acid by HNE in Alzheimer disease brain. *Redox Biol.* 2013, 1, 80–85.
54. Breitzig, M.; Bhimineni, C.; Lockey, R.; Kolliputi, N. 4-Hydroxy-2-nonenal: A critical target in oxidative stress? *Am. J. Physiol. Cell Physiol.* 2016, 311, 537–543.
55. Wong, A.; Dukic-Stefanovic, S.; Gasic-Milenkovic, J.; Schinzel, R.; Wiesinger, H.; Riederer, P.; Münch, G. Anti-inflammatory antioxidants attenuate the expression of inducible nitric oxide synthase mediated by advanced glycation endproducts in murine microglia. *Eur. J. Neurosci.* 2001, 14, 1961–1967.
56. Dinicola, S.; Proietti, S.; Cucina, A.; Bizzarri, M.; Fuso, A.J.A. Alpha-Lipoic Acid Downregulates IL-1 $\beta$  and IL-6 by DNA Hypermethylation in SK-N-BE Neuroblastoma Cells. *Antioxidant* 2017, 6, 74.
57. Schwartz, L.; Abolhassani, M.; Guais, A.; Sanders, E.; Steyaert, J.M.; Campion, F.; Israël, M. A combination of alpha lipoic acid and calcium hydroxycitrate is efficient against mouse cancer models: Preliminary results. *Oncol. Rep.* 2010, 23, 1407–1420.
58. Na, M.H.; Seo, E.Y.; Kim, W.K. Effects of alpha-lipoic acid on cell proliferation and apoptosis in MDA-MB-231 human breast cells. *Nutr. Res. Pract.* 2009, 3, 265–271.
59. Ganapathy-Kanniappan, S.; Geschwind, J.F. Tumor glycolysis as a target for cancer therapy: Progress and prospects. *Mol. Cancer* 2013, 12, 152.
60. Zhang, C.; Liu, J.; Liang, Y.; Wu, R.; Zhao, Y.; Hong, X.; Lin, M.; Yu, H.; Liu, L.; Levine, A.J.; et al. Tumour-associated mutant p53 drives the Warburg effect. *Nat. Commun.* 2013, 4, 2935.
61. Feueracker, B.; Pirsig, S.; Seidl, C.; Aichler, M.; Feuchtinger, A.; Bruchelt, G.; Senekowitsch-Schmidtke, R. Lipoic acid inhibits cell proliferation of tumor cells in vitro and in vivo. *Cancer Biol. Ther.* 2012, 13, 1425–1435.
62. Jeon, M.J.; Kim, W.G.; Lim, S.; Choi, H.J.; Sim, S.; Kim, T.Y.; Shong, Y.K.; Kim, W.B. Alpha lipoic acid inhibits proliferation and epithelial mesenchymal transition of thyroid cancer cells. *Mol. Cell. Endocrinol.* 2016, 419, 113–123.

63. Yang, L.; Wen, Y.; Lv, G.; Lin, Y.; Tang, J.; Lu, J.; Zhang, M.; Liu, W.; Sun, X.  $\alpha$ -Lipoic acid inhibits human lung cancer cell proliferation through Grb2-mediated EGFR down regulation. *Biochem. Biophys. Res. Commun.* 2017, 494, 325–331.
64. Mounjaroen, J.; Nimmannit, U.; Callery, P.S.; Wang, L.; Azad, N.; Lipipun, V.; Chanvorachote, P.; Rojanasakul, Y. Reactive oxygen species mediate caspase activation and apoptosis induced by lipoic acid in human lung epithelial cancer cells through Bcl-2 down-regulation. *J. Pharmacol. Exp. Ther.* 2006, 319, 1062–1069.
65. Dozio, E.; Ruscica, M.; Passafaro, L.; Dogliotti, G.; Steffani, L.; Marthyn, P.; Pagani, A.; Demartini, G.; Esposti, D.; Frascini, F.; et al. The natural antioxidant  $\alpha$ -lipoic acid induces p27(Kip1)-dependent cell cycle arrest and apoptosis in MCF-7 human breast cancer cells. *Eur. J. Pharmacol.* 2010, 641, 29–34.
66. Wenzel, U.; Nickel, A.; Daniel, H.  $\alpha$ -Lipoic acid induces apoptosis in human colon cancer cells by increasing mitochondrial respiration with a concomitant O<sub>2</sub>-\* generation. *Apoptosis* 2005, 10, 359–368.
67. Trivedi, P.P.; Jena, G.B. Role of  $\alpha$ -lipoic acid in dextran sulfate sodium-induced ulcerative colitis in mice: Studies on inflammation, oxidative stress, DNA damage and fibrosis. *Food Chem. Toxicol.* 2013, 59, 339–355.
68. Tripathy, J.; Tripathy, A.; Thangaraju, M.; Suar, M.; Elangovan, S.  $\alpha$ -Lipoic acid inhibits the migration and invasion of breast cancer cells through inhibition of TGF $\beta$  signaling. *Life Sci.* 2018, 207, 15–22.
69. Lee, W.J.; Song, K.H.; Koh, E.H.; Won, J.C.; Kim, H.S.; Park, H.S.; Kim, M.S.; Kim, S.W.; Lee, K.U.; Park, J.Y.  $\alpha$ -Lipoic acid increases insulin sensitivity by activating AMPK in skeletal muscle. *Biochem. Biophys. Res. Commun.* 2005, 332, 885–891.
70. Bitar, M.S.; Ayed, A.K.; Abdel-Halim, S.M.; Isenovic, E.R.; Al-Mulla, F. Inflammation and apoptosis in aortic tissues of aged type II diabetes: Amelioration with lipoic acid through phosphatidylinositol 3-kinase/Akt-dependent mechanism. *Life Sci.* 2010, 86, 844–853.
71. Rochette, L.; Ghibu, S.; Muresan, A.; Vergely, C.  $\alpha$ -Lipoic acid: Molecular mechanisms and therapeutic potential in diabetes. *Can. J. Physiol. Pharmacol.* 2015, 93, 1021–1027.
72. Smith, A.R.; Hagen, T.M. Vascular endothelial dysfunction in aging: Loss of Akt-dependent endothelial nitric oxide synthase phosphorylation and partial restoration by (R)- $\alpha$ -lipoic acid. *Biochem. Soc. Trans.* 2003, 31, 1447–1449.
73. Artwohl, M.; Muth, K.; Kosulin, K.; de Martin, R.; Holzenbein, T.; Rainer, G.; Freudenthaler, A.; Huttary, N.; Schmetterer, L.; Waldhausl, W.K.; et al. R-(+)- $\alpha$ -lipoic acid inhibits endothelial cell apoptosis and proliferation: Involvement of Akt and retinoblastoma protein/p27. *Am. J. Physiol. Endocrinol. Metab.* 2007, 293, 681–689.
74. Zhang, W.J.; Wei, H.; Hagen, T.; Frei, B.  $\alpha$ -Lipoic acid attenuates LPS-induced inflammatory responses by activating the phosphoinositide 3-kinase/Akt signaling pathway. *Proc. Natl. Acad. Sci. USA* 2007, 104, 4077–4082.
75. Kawabata, T.; Packer, L.  $\alpha$ -Lipoic acid can protect against glycation of serum albumin, but not low density lipoprotein. *Biochem. Biophys. Res. Commun.* 1994, 203, 99–104.
76. Thirunavukkarasu, V.; Nandhini, A.A.T.; Anuradha, C.V. Lipoic acid improves glucose utilisation and prevents protein glycation and AGE formation. *Die Pharm.* 2005, 60, 772–775.
77. Quinn, J.F.; Bussiere, J.R.; Hammond, R.S.; Montine, T.J.; Henson, E.; Jones, R.E.; Stackman, R.W. Chronic dietary  $\alpha$ -lipoic acid reduces deficits in hippocampal memory of aged Tg2576 mice. *Neurobiol. Aging* 2007, 28, 213–225.
78. Suh, J.H.; Zhu, B.Z.; de Szoeki, E.; Frei, B.; Hagen, T.M. Dihydrolipoic acid lowers the redox activity of transition metal ions but does not remove them from the active site of enzymes. *Redox Rep.* 2004, 9, 57–61.
79. Micili, S.C.; Goker, A.; Kuscu, K.; Ergur, B.U.; Fuso, A.J.R.S.  $\alpha$ -Lipoic Acid Vaginal Administration Contrasts Inflammation and Preterm Delivery in Rats. *Reprod. Sci.* 2019, 26, 128–138.