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Short review

Lipoic acid as a revolutionary treatment: short review

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Abstract:

Lipoic acid (LA) is widely used as a supplement and remains of interest due to its free radicals scavenging and anti-inflammatory properties. It is a natural substance produced by the mitochondria that has the ability to function not only in water but also in adipose tissues. It can be rapidly absorbed from the gastro-intestinal tract and function in both the cytoplasm and cell membrane due to its hydrophilic and hydrophobic properties. There are two isomers of LA that can be synthesized. Some advantages of LA are that it has the ability to reduce diabetic symptoms, improve endothelial-dependent flow-mediated vasodilation and neurologic disorders, act as an antihypertensive, and be used in the treatment of Alzheimer′s and cancers. Therefore, this work aimed to give brief about LA as an antioxidant supplement in the management of diseases. Sources, chemical composition, endogenous biosynthesis, exogenous manufacture, antioxidant, anti-inflammatory, and therapeutic benefits, both direct and indirect, as an ameliorative agent for chronic and oxidative stress associated diseases are covered in this review.

Keywords: anti-inflammatory; antioxidant; chronic diseases; lipoic acid.

1- Introduction

For several decades, many clinical trials and experimental studies were conducted to authorise the use of natural substances that have antioxidant capabilities in fighting chronic diseases. For this reason, lipoic acid (LA) as a natural compound with antioxidant and anti-inflammatory actions is of interest. It seems that the biochemical properties of LA and its reduced form, dihydrolipoic acid (DHLA), include those of biological antioxidants, metal chelators, endogenous antioxidants regenerator, and anti-inflammatory mediator **(Rochette et al., 2013)**. LA and its reduced form (DHLA) are reviewed here to briefly summaries LA's ability to be used as a revolutionary treatment for chronic diseases due to its characteristics that fight inflammation and free radicals.

1. Lipoic acid

Thioctic acid is another name for lipoic acid (LA), which has the chemical formula 1,2-dithiolane-3-pentanoic acid ($C_8H_{14}O_2S_2$). It is a vitamin-like substance that has been identified as a potent micronutrient with numerous biological functions **(Kim et al., 2013)**.

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The naturally occurring substance LA is created by combining cysteine and octanoic acid in the mitochondrion of plants and animals **(Reed, 2001)**. LA is thought to be a powerful antioxidant, and unlike other antioxidants that only function in water or adipose tissues, LA is found acting in both water and fat **(Szelag et al., 2012)**.

1.1. Occurrence and chemical composition of lipoic acid (LA)

LA comprises eight carbon atoms with a di-thiolane ring, two sulphur atoms, and a carboxylic acid group. The two sulphur groups can be reduced and known as di-hydrolipoic acid (DHLA) or oxidized and referred to as lipoic acid **(Kramer and Packer, 2001)**. There are two forms of LA **(Fig. 1)**, according to the position of the ring structure. The two isomer forms can be produced synthetically but, only the R (+) form of lipoic acid occurs naturally **(Rochette et al., 2015)**.

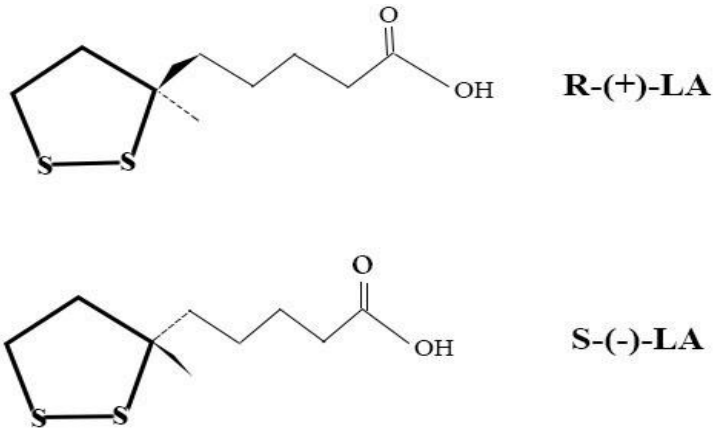

Fig. (1): *Chemical isomers of LA*

R (+) lipoic is found in food sources and is naturally bonded covalently to the amino acid lysine in proteins (lipoyllysine). Although lipoic acid comes from a wide variety of nutrients derived from both plant and animal sources, lipoyl lysine, which is found in broccoli, tomatoes, and spinach, is the most common herbal source of R-LA. However, the liver, heart, and kidney have the highest levels of LA in the animal tissues **(Rochette et al., 2015)**.

1.2. Biosynthesis

1.2.1. Biological synthesis

Lipoic acid is synthesised in the mitochondria from an 8-carbon fatty acid (octanoic acid), **(Fig.2)** where the acyl-carrier protein (ACP) acts as an enzyme cofactor in the production of fatty acids **(Cicchillo et al., 2005 and Zhao et al., 2003)**. The H protein of the glycine cleavage system's H protein helps in the transfer of the octanoyl moiety from octanoyl-ACP to a preserved lysine. The next step is the addition of two sulphur atoms to the protein's H-bound octanoyl moiety at positions 6 and 8, resulting in the formation of a dihydrolipoyl moiety. Afterward, an enzyme made of iron-sulfur clusters induced sulphide atoms. Finally, the dihydrolipoyl moiety is transferred from the H protein of the glycine cleavage system to preserved lysine residues of the E2 components of the multienzyme complexes of ketoacid dehydrogenase by the enzyme lipoyl transferase 1. A dihydrolipoamide dehydrogenase catalyses the oxidation of the dihydrolipoyl moiety.

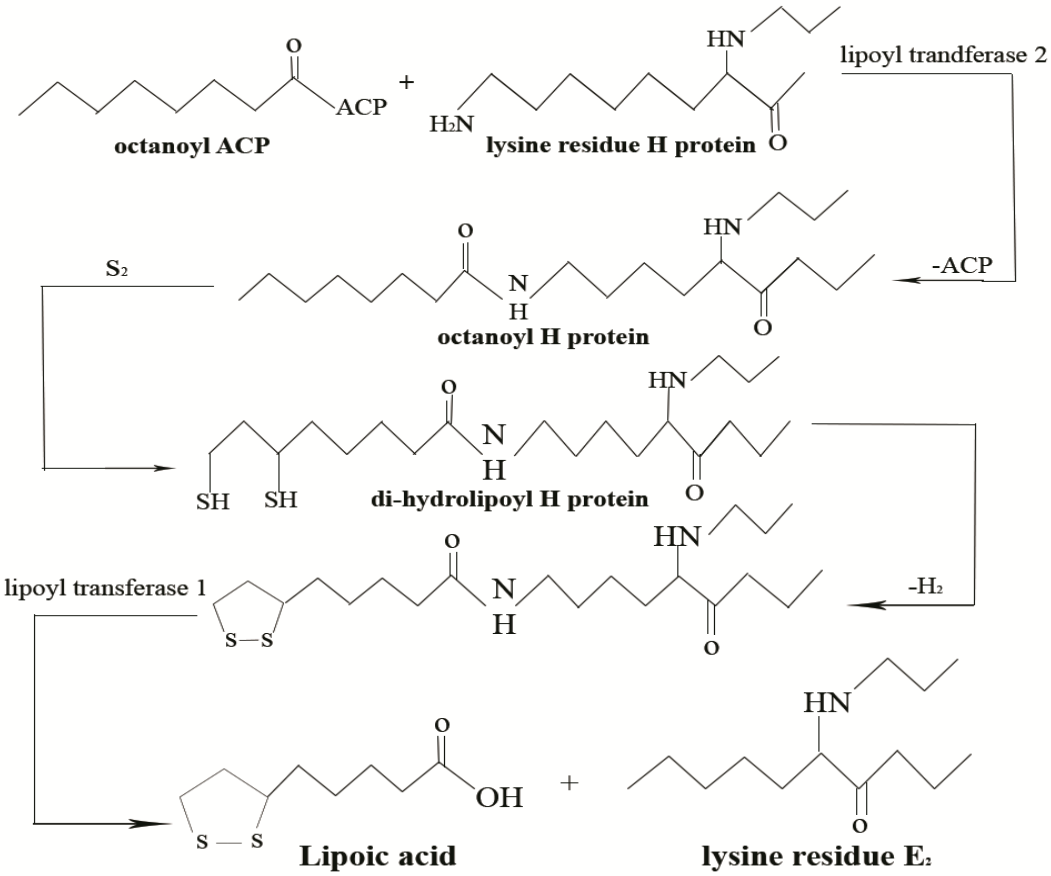

Fig. (2): *LA biosynthesis*

1.2.2. Exogenous manufacture

The first manufacture of lipoic acid was described by Golding **(Brookes et al, 1983)**, who launched the reaction using but-3-enyl magnesium chloride with malic acid and lithium chlorocuprate as catalysts **(Fig. 3)** followed by esterification and debenzylation to produce diol ester, then hydroboration and oxidation to acid to produce dibenzyl acid. This diol underwent further mesylation and sodium sulphide treatment. To get lipoic acid, methyl lipoate was first decomposed with aqueous NaOH.

Later, Golding **(Brookes et al., 1988)** manufactured the R-isomer from S-malic acid through an arrangement overturn at oxirane **(Fig. 4)**. The (R)-oxirane was cleaved using cuprate catalysis to yield (S)-1-(phenylmethoxy) oct-7-en-3-ol. In order to produce (R)-lipoic acid, olefin was converted into methyl-(S)-6,8-dihydroxyoctanoate and then subjected to customary reactions. Similar transformations were made from (S)-oxirane to (S)-lipoic acid.

1.3. Metabolism of lipoic acid

Both hydrophilic and hydrophobic characteristics apply to LA. For that reason, it can exert its functions in both the plasma membrane and the cytoplasm; it can also freely pass through the blood-brain barrier. LA can pass through cell membranes in a variety of ways, including the Na^+-dependent vitamin transport system, the medium-chain fatty acid transporter, and the H^+-linked monocarboxylate transporter. When LA is induced in the body through the diet, it is concentrated in several tissues and subsequently converted by a lipoamide dehydrogenase to DHLA **(Packer et al. 2001)**. Regarding the metabolism of LA and DHLA, similarly rapid tissue

uptake into the liver, brain, heart, and skeletal muscle, in addition to glomerular filtration and renal excretion, follow the quick gastrointestinal transit of LA into the blood **(Schupke et al., 2001)**.

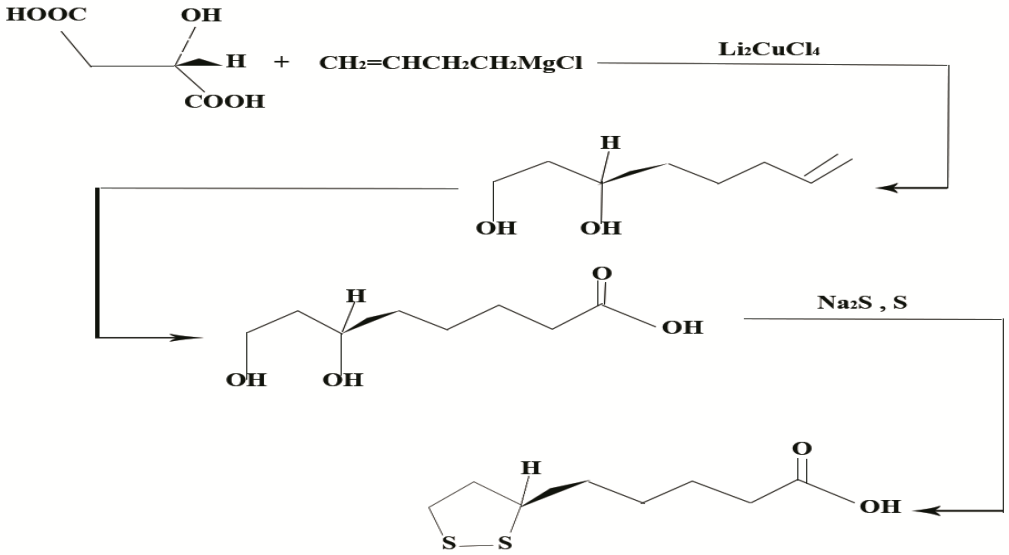

Fig. (3): *LA manufacture*

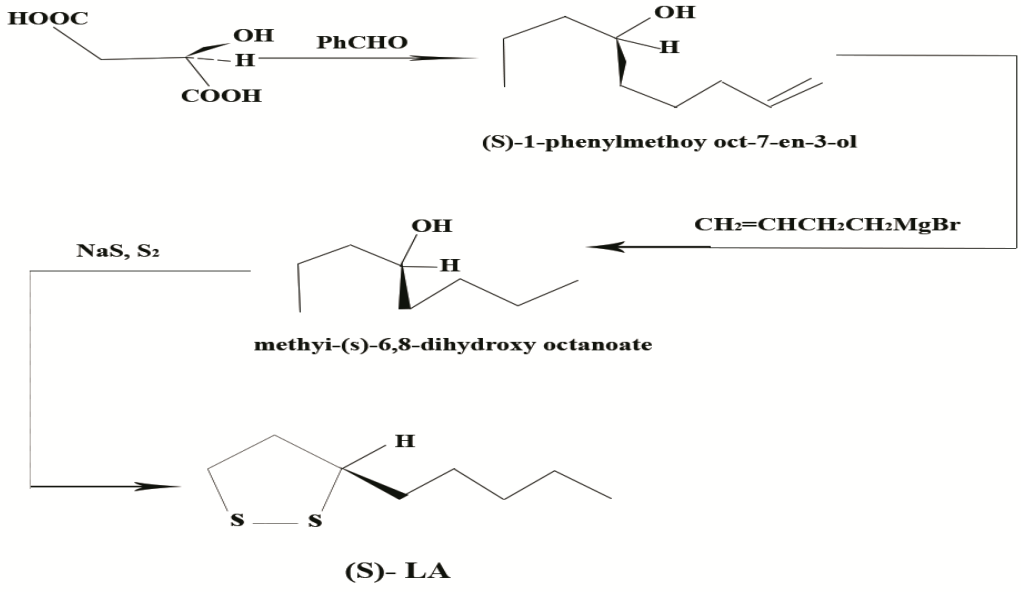

Fig. (4)*: S-*isome *manufacture*

Thioredoxin reductase, lipoamide dehydrogenase, and glutathione reductase are NAD (P) H-driven enzymes that may efficiently reduce LA to DHLA within the cell. DHLA is then released into the extracellular environment to mimic the activity of disulfide reductases **(May et al., 2007).** While the glutathione/glutathione disulfide (GSH/GSSG), thioredoxin reduced/oxidized, and cysteine/cysteine couples and their ability to control cysteine and methionine moieties in proteins are usually associated with the intracellular redox status **(Packer et al., 2001)**.

2. Benefit properties of alpha-lipoic acid

2.1.Antioxidant properties

LA plays a vital role in mitochondrial dehydrogenase interactions, but free LA has not been found in human beings because it is generally bound to proteins. However, after therapeutic submissions, it can be found in the circulation **(El-Beshbishy et al., 2011)**. The molecular nature of LA clarifies its antioxidant capability and ability to chelate toxic metals **(Al Abdan, 2012)**. There are several mechanisms by which LA protects the cell against oxidative damage. One of these mechanisms is the removal of free radicals through enzymatic activities via the cytoplasmic or mitochondrial scavenger enzymes such as superoxide dismutase (SOD). Another pathway of protection is interaction with free radicals, which makes them less active by giving them the missing electron **(Fig. 5) (Grasso et al., 2014)**.

Furthermore, LA is able to chelate iron, copper, and other transition metals to establish stable complexes. Also, it is able to prevent the oxidation of ascorbic acid and suppress the lipid peroxidation catalyzed by copper **(Gomes and Negrato, 2014)**. Previous research has found that incorporating LA into diets can boost antioxidant effects **(Zhang et al., 2009; Chen et al., 2011; Bai et al., 2012)**. In light of the mentioned antioxidant mechanisms, one might hypothesise that a substance functions as both a direct and/or indirect antioxidant **(Rochette et al., 2015)**.

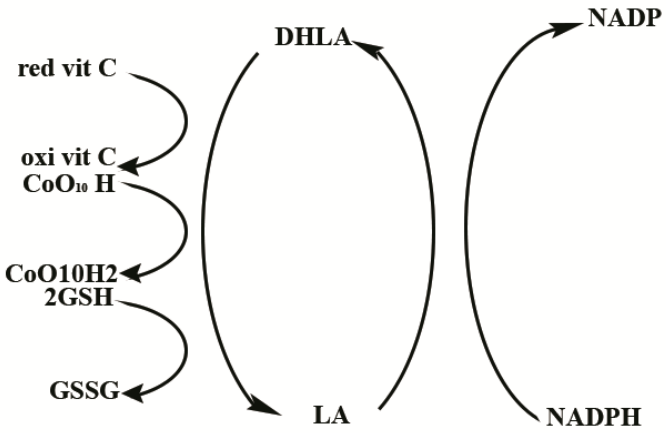

Fig. (5): *anti-oxidative function of LA*

2.1.1. Lipoic acid as direct antioxidant

Early research revealed that LA and DHLA scavenge singlet oxygen ($1O_2$), hypochlorous acid (ClO^-), and hydroxyl radicals (OH^-) **(Packer et al., 1995)**. Recently, it was shown that peroxynitrite (ONOO), the primary mediator of nitric oxide's cytotoxic effects, reacts with LA and DHLA **(Trujillo and Radi 2002)**. Numerous studies have demonstrated that taking LA supplements causes oxidative stress to decrease and other antioxidant properties, like those of vitamins C and E, to regenerate. The ability of LA and DHLA to lower the oxidized forms of other antioxidants is another crucial role they play **(Petersen Shay et al. 2008)**.

2.1.2. Lipoic acid as indirect antioxidant

LA/DHLA can chelate divalent transient metal ions, due to the presence of two thiol groups, to combine with Mn^{2+}, Cu^{2+}, Fe^{2+}, and Zn^{2+} to form stable complexes without any metal

depletion. Several studies have revealed that LA and DHLA are reactive to metals. Furthermore, the R-enantiomer showed greater affinity than metal chelation's S-enantiomer **(Suh et al., 2004)**.

2.2.Anti-inflammatory properties

Numerous confirmations suggest that by controlling the expression of genes linked to anti-oxidative and anti-inflammatory signaling, LA restores mitochondrial activity and lowers oxidative stress. Inflammation responses to damaging stimuli are used to try and get rid of them, protect the nearby tissue, and start the healing process. Chronic inflammation that persists, though, also contributes to disease. Increased oxidative stress is crucial for persistent inflammation **(Lee et al., 2006)**.

Similarly, LA inhibits the binding of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and neuclear factor kappa beta (NF-kappa β) to DNA **(Lee et al., 2007)**. LA inhibits NF-kappa β activation and adhesion molecule production caused by TNF-α via antioxidant mechanisms, which is consistent with metal chelator function **(Zhang et al., 2013)**. Similarly, Interleukin-6 (IL-6) is a common inflammation marker that regulates the development of other inflammatory cytokines such as interleukin-1 (IL-1) and TNF-α, and its anti-inflammatory effects in humans have received little attention **(Sola et al., 2005; Ikeda et al., 2001)**. However, the clinical trials are too restricted to be conclusive.

3. Therapeutic effects of LA

Since oxidative stress is involved in the developing of several pathogens, it has been informed that, the effective usage of LA to treat several diseases associated with oxidative stress **(Golbidi et al., 2011)** is because it easily crosses the biological membranes and neutralises the free radicals in both the aqueous and lipid phases, this freely crossing ability is related to its minor size and high lipophilic features. LA's therapeutic activity is not limited to its antioxidant properties, but also to its ability to stimulate signaling cascades **(Guimaraes et al., 2007)**. Currently, LA is widely used as a supplement because of its rapid metabolism, its stability, and its low rate of degradation **(Tibullo et al., 2017)**. Many clinical trials and research studies have shown that LA has therapeutic benefits; as a result, we thought it would be helpful to outline how LA affects a wide range of certain prevalent diseases.

3.1.Diabetes treatment

Diabetes mellitus is best described by hyperglycemia as a result of impaired insulin secretion and/or activity deficiency. It is aware of a group of clinically and genetically manifests metabolic diseases. **(Skyler and Oddo, 2002)**. As a result, numerous clinical trials have been conducted to quantify the ability of LA in reducing diabetic signs, and it demonstrated a significant improvement in patients with diabetic polyneuropathies' lower limbs and feet **(Ziegler et al., 2004)**. LA demonstrated functional usefulness for whole-body glucose tolerance, was beneficial against insulin resistance, and was useful for skeletal muscle glucose absorption in animal models **(Saengsirisuwan et al., 2004)**. In addition, it revealed enhancements in glucose dumping in type 2 diabetic patients **(Cremer et al., 2006)**.

LA has been used as a clinical trial for type 2 *diabetes mellitus* treatment and revealed a promising future as it improved HbA_{1c} and glycemic control **(Udupa et al., 2012)**. Another randomised study showed a reduction in fasting blood sugar and HbA_{1c}. Additionally, indicators of oxidative stress include DNA oxidative damage and lipid peroxidation (LPO), which showed

much amelioration **(Porasuphatana et al., 2012)**. Another trail showed enhancement in lipid fractions and glucose in certain tissues **(de Oliveira et al., 2011)**.

3.2.Treatment of Vascular system disorders

By creating a physical barrier between the blood and the vessel wall, vascular endothelial cells, which line the blood vessel lumen, control blood vessel patency and limit platelet adhesion. Nitric oxide (NO), a gas produced by endothelial nitric oxide synthase (eNOS), regulates the flexibility of the vessel wall. Endothelial dysfunction results from eNOS activity deficits of any kind and is represented by a reduction of vasodilation, a pro-inflammatory milieu, and a prothrombotic state **(Heitzer et al., 2001)**.

LA recovers the plasma's redox status and induces NO-mediated vasodilation that is endothelium-dependent by increasing NO synthesis and increasing the eNOS phosphorylation **(Heitzer et al., 2001; Hagen et al., 2002; Smith et al., 2003)**. Another study showed that, LA induction enhanced endothelial-dependent flow-mediated vasodilation **(Park et al., 2014)**. Nevertheless, more chronic studies are essential to prove the effectiveness of LA as a treatment for vascular endothelial dysfunction.

3.3. Hypotensive effect of

Hypertension is associated with a number of complications, including chronic kidney failure, vascular aneurysms, and stroke. The ability of LA to increase tissue gloutation (GSH) levels and to prevent harmful changes to the sulfhydryl (SH) group in Ca^{2+} channels, which internally regulate systolic blood pressure and Ca^{2+}, are the basis for its rational therapeutic use against hypertension **(Vasdev et al., 2002)**. **El Midaoui and de Champlain (2002)** investigated how LA restored GSH and explained this restoration in terms of superoxide (O^{-2}) synthesis regulation. Additionally, it was claimed that LA prevents the endothelium's vasoconstrictor, renal and vascular endothelin-1 **(Takaoka et al., 2001; Shay et al., 2009)**. In clinical trials, LA induction showed promise as an antihypertensive therapy in patients with metabolic syndrome **(McMackin et al., 2007)**.

3.4.Cancer treatment

Aerobic glycolysis is the process by which cancer cells convert glucose to lactate and then produce adenosine triphosphate (ATP). The persistent stimulation of aerobic glycolysis in malignant cells results in the loss of tumor suppressors, which advances the disease. For this reason, inhibiting the aerobic cycle may contribute to anticancer effects **(Ganapathy-Kanniappan et al., 2013)**. **Feuerecker et al. (2012)** found that LA activated pyruvate dehydrogenase in tumor cells, inhibiting cell proliferation, increasing apoptosis in neuroblastoma breast cancer cell lines, and hindering tumor growth **(Jeon et al., 2016).**

Likewise, LA reduced thyroid cancer cell proliferation and growth through activation of adenosine monophosphate-activated protein kinase (AMPK) and inhibition of the mammalian target of rapamycin S6 (mTOR-S6) signaling pathway and suppressed tumor growth. In lung cancer cells, LA suppresses cell proliferation by the action of growth factor receptor-bound protein 2 (GRB2)-mediated estimated glomerular filteration rate (eGFR) reduction **(Yang et al. 2017)**. Numerous studies revealed that, in cancer cells, LA has the ability to initiate the mitochondrial pathway of apoptosis. LA has recently been shown to inhibit metastatic breast cancer cell migration via extracellular signal-regulator protein kinases 1 and 2 (ERK1/2) and protein kinase beta (PKβ) signaling **(Moungjaroen et al., 2006)**.

3.5.Nonalcoholic fatty liver disease

The most typical liver disease is thought to be non-alcoholic fatty liver disease (NAFLD). In the metabolic syndrome, obesity, diabetes, and dyslipidemia, NAFLD is frequently present. Inflammation, oxidative stress, and mitochondrial dysfunction are the three primary factors in the pathophysiology of NAFLD **(Lazo and Clark, 2008)**. Various studies suggest the action of LA in NAFLD. In addition to increasing the markers of inflammation and innate immune activation, LA also improved the levels of insulin, free fatty acids, glucose, and triglycerides **(Jung et al., 2012).** Also, LA increased uncoupling protein 2 (UCP2), which suppresses the electron transport chain, leading to inhibited ATP synthesis **(Chen et al., 2012).**

3.6.Treatment of neurological disorders

Concerning the properties of LA in the central nervous system (CNS), clinical studies have demonstrated an anti-inflammatory effect as well as the ability to prevent neuronal damage brought on by an imbalance of reactive oxygen species (ROS) **(Maczurek et al., 2008)**. LA's anti-inflammatory effects are linked to the inhibition of nuclear factor kappa beta (NF-β), a family of transcription factors involved in the production of inflammation genes that control ROS amount and apoptosis **(De Araújo et al., 2011).** Furthermore, LA increased norepinephrine and dopamine levels via unidentified pathways to change brain acetylcholine-esterase activity **(Silva et al., 2013)**.

3.7.Treatment of Alzheimer's disease

Alzheimer's disease (AD) is a neurological condition characterised by changes in cognition, function, and behavior. The formation of beta-amyloid (A) plaques and the rise in TAU have both been linked to memory loss **(Wu et al., 2018)**. Significant evidence has supported the hypothesis that oxidative stress contributes to the pathophysiology of AD **(Huang et al., 2016)**. The use of numerous anti-inflammatory medications has been advocated for the treatment of AD and other neurodegenerative illnesses. But prolonged dosage could result in gastrointestinal toxicity **(Cacciatore et al., 2016)**.

By protecting cortical neurons from cytotoxicity caused by A or H_2O_2 **(Zhang and Frei, 2001)**, which is partially recognized by the activation of the PK signaling pathway, LA has been designated as an AD treatment with neuro-protective characteristics on A-mediated cytotoxicity **(Ono et al., 2006; Lovell et al., 2003).** Additional studies showed that, by activating choline acetyl-transferase, which provides more acetyl-CoA for acetylcholine ACh generation, LA increased ACh synthesis and demonstrated anti-AD benefits **(Holmquist et al., 2007).** According to **Haugaard and Levin (2000)**, DHLA greatly enhanced choline acetyl-transferase activity, causing it to completely disappear. The authors came to the conclusion that it might serve as a coenzyme in the choline acetyltransferase reaction as a result.

Furthermore, it has been demonstrated that the inflammatory process that results in the production of amyloid plaques is marked by increased amounts of free radicals and pro-inflammatory cytokines **(Meraz-Ros et al., 2013)**. LA serves as a scavenger of ROS and raises GSH levels **(Suh et al. 2014).** Similar to this, **Dinicola et al. (2017)** discovered that LA modulated DNA methylation-dependent modulation to reduce the levels of the inflammatory cytokines interleukin-1 beta (IL-1β) and IL-6 in neuroblastoma cells.

4. Summary and future directions

LA and DHLA possess many biological functions, including acting as antioxidants via metal chelation and endogenous antioxidant regeneration. Moreover, many studies have stated that LA

can control the oxidant and inflammatory pathways. Likewise, in both the prevention and treatment of a number of experimental disorders and clinical studies, LA continues to have a number of therapeutic effects. Future disease prevention and treatment plans may incorporate a combination of naturally occurring antioxidant chemicals.

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