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REVIEW ARTICLE

α-Lipoic Acid and its Role on Female Reproduction

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Abstract: α-lipoic Acid (ALA), also known as thioctic acid, is a biological thiol present in all types of prokaryotic and eukaryotic cells. It has been shown that ALA or its reduced form, DHLA, has several positive effects on human health, acting as a biological antioxidant, metal chelator and detoxifying agent. It is able to reduce the oxidation of several antioxidant agents like glutathione, vitamins C and E, and modulate insulin and NF-kB signaling pathways. ALA's pharmacological effects are not only related to its antioxidant properties but it shows an anti-inflammatory action. In particular, ALA is able to reduce inflammasome activity, the pro-inflammatory cytokine levels, such as TNF-α, IL-1β, IL-6, IL-18 and IL-17, interferon (INF)-γ as well as the production of Vascular and Intercellular cell adhesion protein (VCAM-1 and ICAM-1). In recent papers, ALA has been indicated as a possible therapeutic approach to several endocrine or inflammatory disorders affecting female reproduction. Aim of the current review was to assess whether ALA has an evidence-based beneficial role on gynecological and obstetrical diseases such as polycystic ovary syndrome (PCOS), endometriosis, and miscarriage.

Keywords: α-Lipoic acid (ALA), endometriosis, polycystic ovary syndrome (PCOS), miscarriage, recurrent pregnancy loss (RPL), inflammation.

1. INTRODUCTION

Alpha-lipoic Acid (ALA), also known as thioctic acid or 1,2-dithiolane-3-pentanoic acid, is a naturally occurring compound synthesized enzymatically from octanoic acid and cysteine in animal and plant mitochondria. It shows two enantiomeric configurations (*R*-ALA and *S*-ALA) and its reduced form is known as dihydrolipoic acid (DHLA) (Fig. **1**) [1, 2]. 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 [2, 3].

ALA is mainly known for its potent antioxidant activity, but it shows several other properties, including anti-inflammatory activity, chelation of metal ions and lipid and glucose metabolism modulation [4-6]. Furthermore, ALA can regulate multiple signaling transduction pathways, such as nuclear factor kappa B (NF-kB), nitric oxide synthesis, insulin, and cellular apoptosis [7].

There are evidences demonstrating that ALA shows therapeutic activity in particular conditions and diseases, including obesity, diabetes, diabetic neuropathy, multiple sclerosis, schizophrenia, and cancer [2]. Recently, ALA has been suggested as a possible therapeutic approach for several endocrine or inflammatory disorders that affect female reproduction. It is well known that hormones and inflammatory mechanisms are involved in several female reproductive functions, including ovulation, menstruation, embryo implantation and pregnancy [8]. All these events are finely orchestrated by specific molecular pathways involving growth factors, chemokines, cytokines and lipid mediators and an imbalance between pro- and anti-inflammatory microenvironment can account for mechanisms implicated in the pathogenesis and/or progression of pathological states, like endometriosis, uterine myomas, polycystic ovary syndrome (PCOS), and other reproductive disorders [9]. Furthermore, an increased inflammation might lead to derangements of the immune-endocrine cross talk between the endometrium and trophoblast, predisposing to pregnancy complications such as early pregnancy loss, abnormal placentation and hypertensive disorders [8].

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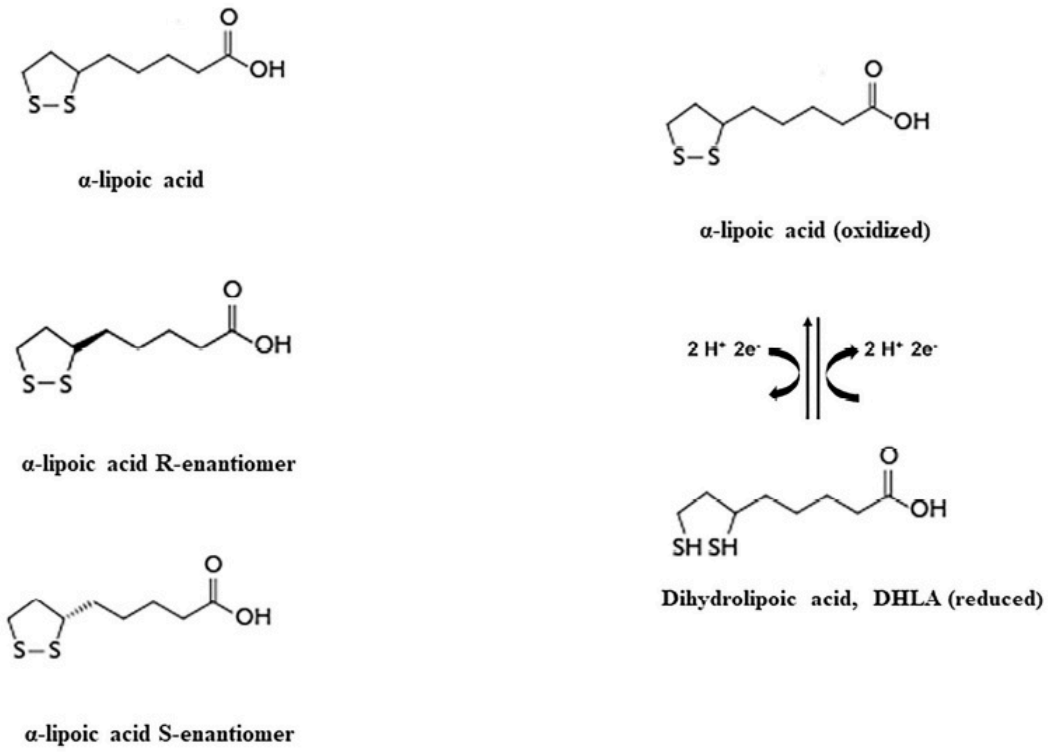

Fig. (1). Alpha-lipoic acid (ALA) structure. ALA contains two thiol (sulfur) groups, which may be oxidized or reduced. It has two enantiomeric configurations (R-ALA and S-ALA), and its reduced form is known as dihydrolipoic acid (DHLA).

For all these reasons, we decided to examine the role of ALA as a molecule modulating inflammation in the female reproductive tract and evaluate its effects in gynecological disorders and obstetrical complications.

2. POLYCYSTIC OVARY SYNDROME (PCOS)

Polycystic Ovary Syndrome (PCOS) is a common endocrine disease of the reproductive age, affecting 4-7% of women. Clinical and biochemical signs are hyperandrogenism, chronic anovulation, and polycystic ovary morphology. Oxidative Stress (OS), chronic low-grade inflammation, and Insulin Resistance (IR) are frequent findings in PCOS that are augmented by concomitant obesity [10-13]. Growing evidence demonstrate that PCOS has a negative impact on fertility, on pregnancy outcome, and it is associated with an increased risk of pregnancy complications, including early pregnancy loss, Gestational Diabetes (GDM) and Preterm Birth (PTB) [14-16].

Recently, ALA has been considered a possible therapeutic approach for PCOS and IR [17, 18]. In addition to its potent antioxidant activity, ALA is able to increase glucose utilization through the activation of adenosine monophosphate-activated protein kinase (AMPK), a cellular energy sensor that induces the translocation of Glucose Transporter-4 (GLUT-4) to the plasma membrane [19].

Clinical trials reported that ALA, alone or associated with inositol, is able to improve glucose control, IR, metabolism, and endocrine parameters in PCOS patients acting as insulin sensitizers and antioxidant agent [20-26]. Inositols (myo-inositol or D-chiroinositol) are intracellular second messengers that regulate the effects of several hormones such as follicle-stimulating hormone (FSH), thyroid-stimulating hormone, and insulin [27]. In a recent paper, Fruzzetti *et al.* evaluated the effects of treatment with ALA (800 mg/day) associated with two different doses of myo-inositol (MI, 1000 mg or 2000 mg/day) on clinical and metabolic features of women with PCOS [19]. They found that this combination is able to restore a normal menstrual cycle in women with PCOS, acting on hormonal and metabolic parameters, with a more evident effect with a higher dose of MI. In another study, Cappelli *et al.* demonstrated that ALA plus MI, in addition to treatment with metformin, an insulin sensitizing drug, showed a better response in terms of reduction of androgen levels, body mass index (BMI) and Homeostasis Model Assessment Index (HOMA index) than metformin alone in women with PCOS [28]. Furthermore, Genazzani *et al.* have shown the efficacy of the administration of ALA at low dosage (400 mg/day) on the hormonal and metabolic pattern in obese PCOS women [22].

Recent studies suggest that inflammation might be one of the potential risk factors of PCOS and inflammatory cytokines and chemokines were considered to be one of the hallmarks in triggering the immune mechanism in PCOS [29]. In particular, it has been reported that women with PCOS show elevated plasma concentrations of inflammato-

ry cytokines, including IL-6 and IL-18, TNF-α, and CRP [29]. Furthermore, chronic inflammation interlinks obesity, insulin resistance, cardiovascular disease, and diabetes that are the metabolic risk markers of PCOS. Therefore, therapeutic strategies trying to reduce the inflammatory cytokines impact on ovarian and metabolic functions play an important role in the treatment of PCOS [30]. Zhang Y *et al.*, observed a decrease in IL-6 and TNF-α concentrations in obese patients with impaired glucose tolerance treated with ALA (600 mg/day) for two weeks [31]. Moreover, ALA treatment (300 mg/day) for four weeks causes a significant decrease in IL-6 and plasminogen activator-1 (PAI-1) plasma levels in patients with metabolic syndrome [32]. Growing evidence indicate that ALA is able to inhibit the translocation of redox-sensitive and pro-inflammatory transcription factor, nuclear factor-kappa B (NFκB), from the cytosol to the nucleus. NF-κB induces the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines, and also participates in inflammasome regulation [33, 34].

Overall, ALA administration, targeting the NFκB signaling pathway, might have several beneficial effects inducing regression of chronic inflammation associated with PCOS and might represent a novel and safe approach as anti-inflammatory therapies.

3. ENDOMETRIOSIS

Endometriosis is an estrogen-dependent pelvic disease affecting 6%~10% of reproductive-aged women worldwide [35, 36]. It is characterized by the presence of endometrial tissue outside the uterine cavity where the implanted cells secrete prostaglandin E2 and multiple cytokines that elicit an inflammatory response [36]. The overexpression of cytokines such as TNF-α, interleukins, TGF-β, monocyte chemoattractant protein-1 [MCP-1], and the resulting chronic inflammation have been shown to contribute to chronic pelvic pain and endometriosis-related infertility [37-39].

Medical treatments for patients with endometriosis include Gonadotropin-releasing Hormone (GnRH) analogues and hormonal contraceptives that are aimed at reducing the production of endogenous estrogens or inducing endometrial differentiation, but these drugs compromise the fertility of the women during their use [40]. An alternative approach for the treatment of endometriosis is represented by anti-inflammatory compounds, but the use of traditional nonsteroidal anti-inflammatory agents (NSAIDs) is not successful for several side effects [40]. A high number of molecules have been tested in preclinical models of endometriosis due to their ability to modulate inflammatory pathways [41]. Among these, ALA was reported to exhibit strong anti-inflammatory activity by inhibiting the NF-κB-induced transcription of a variety of molecules associated with inflammation, vascular adhesion, and monocyte migration, including pro-inflammatory cytokines [42].

A recent study demonstrated that ALA, in combination with N-Acetyl Cysteine (NAC), and bromelain, shows high anti-inflammatory properties both *in vivo* and *in vitro* models of endometriosis [42]. Moreover, in a clinical trial, the combination of NAC, ALA, bromelain and zinc seems also to be effective in the control of endometriosis-associated pelvic pain (EAPP) [43]. Chronic pelvic pain, dysmenorrhea and dyspareunia are typical clinical manifestations of endometriosis and have a negative impact on quality of life.

Han *et al.* have recently demonstrated that the estrogen receptor β (ER-β), which is remarkably high in endometriotic tissues, interacts with components of the inflammasome leading to increased production of IL-1β and IL-18, cytokines involved in endometrial cells adhesion and proliferation [44]. Inflammasomes are immune cytosolic complexes consisting of NLR-family pyrin domain-containing protein (NALP), the apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (ASC), and pro-caspase-1. These complexes regulate the immune response in several types of cells by activating pro-caspase-1 with consequent cleavage of pro-interleukin IL-1β and pro-IL-18 and secretion of their mature forms [45].

Several studies found that both NFκB and mitogen-activated protein kinase (MAPK) signaling contribute to the activation of NALP-3 inflammasome [46, 47]. Kim *et al.* reported that ALA inhibits NF-κB translocation to the nucleus and MAPK signaling molecules, such as p-ERK and p-p38, with a consequent reduction of NALP-3 inflammasome, cleaved/active caspase-1expression and pro-inflammatory cytokine release [48].

The key role of inflammasome NALP-3 in the pathogenesis of endometriosis was highlighted by the observation that ectopic endometrial lesion volumes were greatly reduced in a model of NALP-3 deficient mice [44].

Since NALP-3 plays a critical role in inflammation-mediated human diseases and represents a promising drug target for new anti-inflammatory therapies, we recently investigated the effect of ALA on NALP-3 inflammasome expression/activation in endometriotic cell lines.

We demonstrated that ALA is able to inhibit endometriosis progression *in vitro* by reducing ER-β expression, NALP-3 inflammasome expression/activaction, and IL-1β and IL-18 cytokine secretion [49]. Furthermore, in our experiments on epithelial and stromal endometriotic cell lines, ALA treatment is able to reduce cellular adhesion and invasion *via* a lower expression of adhesion molecules (I-CAM) and MMPs activities [49]. All these findings suggest that ALA can inhibit the inflammatory response in endometriosis by regulating the immune response associated with NFkB signaling and NALP-3 inflammasome activation.

4. PREGNANCY COMPLICATIONS

Pregnancy is a dynamic state involving cellular, metabolic and vascular adaptations that are crucial to support fetus development and growth [50]. A regulated inflammatory response is required in any phase of pregnancy, from implantation and placental formation, to the development of the semi-allogeneic fetus, until delivery [51]. Several studies showed that uncontrolled or excessive inflammation repre-

sents a significant risk factor for pregnancy complications such as pregnancy loss, preterm birth, fetal growth restriction and preeclampsia [52].

Since ALA seems to be a fine modulator of many pivotal molecular pathways showing high anti-inflammatory properties, its supplementation has been recently proposed in some clinical trials to study the efficacy in preventing pregnancy loss.

Porcaro *et al.* carried out a clinical trial in pregnant women with threatened miscarriage. By monitoring the main clinical signs such as chorioamniotic separation, subchorionic hematoma, vaginal bleeding, abdominal pain, they found that ALA supplementation (600 mg by oral route) improved the standard treatment with progesterone vaginal suppositories [53]. Furthermore, a recent trial pilot study comparing the therapeutic efficacy of ALA *vs.* progesterone, by vaginal route, demonstrated that the subchorionic hematoma had a significantly quicker resorption in women treated with ALA, than in those treated with progesterone [54].

Finally, in a retrospective observational study, Parente *et al.* showed the safety of oral ALA treatment in pregnant women. They found that the dose of 600 mg/day, for 20 weeks or more, did not bring out any adverse effect both in mothers and newborns [55].

To date, ALA has been successfully used in patients with pregnancy complications, even though the mechanisms by which it protects, early pregnancy remains poorly understood.

4.1. Recurrent Pregnancy Loss

Recurrent pregnancy loss (RPL) is defined as two or more consecutive clinical pregnancy losses prior to 20 weeks of gestation, is the most common pregnancy complication, and approximately 5%-15% of all pregnancies can be affected [56].

Starting from implantation through gestation, the crosstalk between inflammatory and anti-inflammatory signaling, hormonal changes, and cellular events are central to normal pregnancy outcomes [57]. There is evidence that the dynamic endometrial balance between pro-inflammatory and anti-inflammatory mediators required for a normal pregnancy is altered in RPL patients [58-62].

It has been shown that premature or aberrant activation of NFkB impairs pregnancy [63]. NFκB, as a key regulator of many pro-inflammatory cytokines, exhibits an increase in the endometrium during early pregnancy, indicating that its activation is closely related to the inflammatory microenvironment of the uterus in early pregnancy [64, 65].

ALA is able to modulate NFkB activity by preventing the degradation of IkB through the modulation of upstream kinases like MAPK or by its capacity to regenerate vitamin E resulting in inhibition of protein kinase C, which is also able to phosphorylate IkB [7].

Furthermore, it has been demonstrated that ALA also activates the dissociation of nuclear factor erythroid-2–related factor 2 (Nfr-2) from its regulator Kelchlike ECH-associated protein 1 (Keap 1) and allows its translocation to the nucleus [18]. Nfr-2 is able to increase the expression of anti-inflammatory and antioxidant genes. The key role of Nrf2 in pregnancy has been confirmed in Nrf2 knockout mice that suffer from placental oxidative stress and show decreased fetal growth [66].

Recently, we noticed that abnormal inflammasome NALP-3 activation, in the absence of detectable infectious causes, might be another molecular mechanism involved in establishing an unreceptive endometrium, potentially leading to early fetal loss [54]. Moreover, we showed that in women with a history of idiopathic RPL, ALA plus myoinositol supplementation for three-month significantly reduced the endometrial inflammasome NALP-3 expression and activation [67]. Then, by *in vitro* experiments with endometrial explants obtained from these RPL patients, we demonstrated that ALA, but not myoinositol, is able to reduce endometrial inflammasome activity and the consequent pro-inflammatory cytokines (IL-18 and Il-1β) secretion [67].

By taking together all these observations, ALA seems to contribute strongly to counteracting many alterations involved in pregnancy losses.

CONCLUSION

Recently, ALA has been suggested as a new therapeutic approach for several endocrine or inflammatory disorders affecting female reproduction. As described in Fig. (**2**), ALA is able to:

a) Increase glucose utilization through the activation of adenosine monophosphate-activated protein kinase (AMPK), a cellular energy sensor that induces the translocation of Glucose Transporter-4 (GLUT-4) to the plasma membrane.

b) Inhibit the translocation of redox-sensitive and pro-inflammatory transcription factor, nuclear factor-kappa B (NFκB), from the cytosol to the nucleus. NFκB induces the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines.

c) Reduce the pro-inflammatory cytokine levels, such as TNF-α, IL-1β, -6, -8 and -17, interferon (INF)-ɤ as well as the production of Vascular and Intercellular cell adhesion protein (VCAM-1 and ICAM-1).

d) Reduce NALP-3 inflammasome expression and activation, and pro-inflammatory IL-1β and IL-18 cytokine secretion.

e) Activates the dissociation of Nfr-2 from its regulator Keap 1 and allows its translocation to the nucleus. Nfr-2 increases the expression of anti-inflammatory and anti-oxidant enzymes genes expression.

In conclusion, ALA may be a good candidate and effective therapeutic treatment for the prevention of pathological conditions associated with gynecological or obstetrical diseases. However, more controlled clinical trials should be designed to investigate ALA therapeutic effects on female metabolic, inflammatory and reproductive pathways.

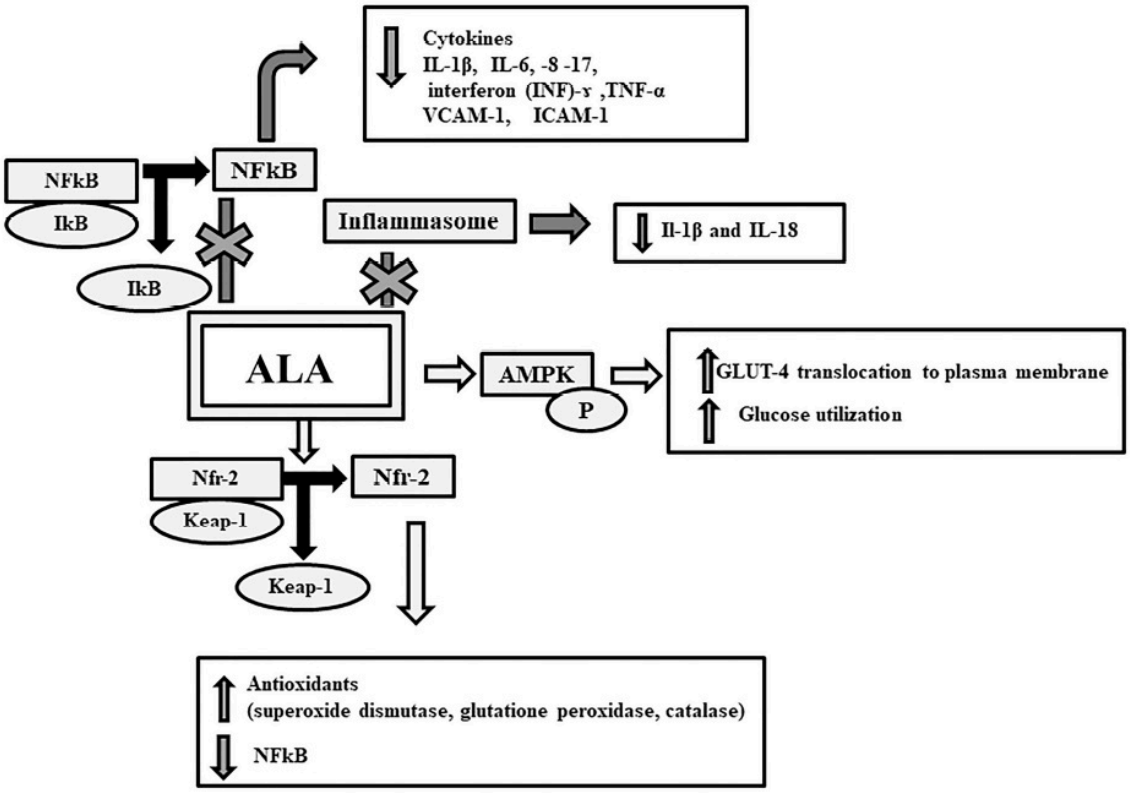

Fig. (2). Schematic view of underlying mechanisms of ALA effects on gynecological and obstetrical diseases. ALA is able to inhibit the translocation of redox-sensitive and pro-inflammatory transcription factor, nuclear factor-kappa B (NFκB), from the cytosol to the nucleus. NF-κB induces the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines, and also participates in inflammasome regulation. ALA reduces the pro-inflammatory cytokine levels, such as TNF-α, IL-1β, -6, -8 and -17, interferon (INF)-ɤ as well as the production of Vascular and Intercellular cell adhesion protein (VCAM-1 and ICAM-1). ALA is able to increase glucose utilization through the activation of adenosine monophosphate-activated protein kinase (AMPK), a cellular energy sensor that induces the translocation of Glucose Transporter-4 (GLUT-4) to the plasma membrane. ALA also activates the dissociation of nuclear factor erythroid-2–related factor 2 (Nfr-2) from its regulator Kelchlike ECH-associated protein 1 (Keap 1) and allows its translocation to the nucleus. Nfr-2 is able to increase the expression of anti-inflammatory and antioxidant genes. ALA reduces NALP-3 inflammasome expression and activation, and pro-inflammatory IL-1β and IL-18 cytokine secretion. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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