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REVIEW ARTICLE

Can alpha-linolenic acid be a modulator of "cytokine storm," oxidative stress and immune response in SARS-CoV-2 infection?

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Abstract

Alpha-linolenic acid (ALA) is a long-chain polyunsaturated essential fatty acid of the Ω3 series found mainly in vegetables, especially in the fatty part of oilseeds, dried fruit, berries, and legumes. It is very popular for its preventive use in several diseases: It seems to reduce the risk of the onset or decrease some phenomena related to inflammation, oxidative stress, and conditions of dysregulation of the immune response. Recent studies have confirmed these unhealthy situations also in patients with severe coronavirus disease 2019 (COVID-19). Different findings (in vitro, in vivo, and clinical ones), summarized and analyzed in this review, have showed an important role of ALA in other various non-COVID physiological and pathological situations

against "cytokines storm," chemokines secretion, oxidative stress, and dysregulation of immune cells that are also involved in the infection of the 2019 novel coronavirus. According to the effects of ALA against all the aforementioned situations (also present in patients with a severe clinical picture of severe acute respiratory syndrome-(CoV-2) infection), there may be the biologic plausibility of a prophylactic effect of this compound against COVID-19 symptoms and fatality.

KEYWORDS
alpha-linolenic acid, COVID-19, cytokine storm, inflammation, oxidative stress, SARS-CoV-2

1 | INTRODUCTION

Alpha-linolenic acid (ALA) (C18:3 $\omega - 3$) (Figure 1) is a long-chain polyunsaturated essential fatty acid of the Ω3 series, precursor of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); ALA is found mainly in vegetables, especially in the fatty part of oilseeds, dried fruit, berries, and legumes (Yuan et al., 2022). ALA is essential for humans' survival, and it cannot be synthesized in the body; hence, ALA must be obtained through the diet or with supplementation (Das, 2006). The composition of an individual's gut microbiota can influence the efficiency of ALA metabolism and the conversion efficiency into EPA and DHA. Certain specific bacteria, such as species of *Bacteroides* and *Bifidobacterium*, have been found to play a role in the conversion of ALA (Costantini et al., 2017). This fatty acid has been demonstrated to exert several biological effects, and it is important in the prevention of many diseases, such as cardiovascular pathologies, interfering in the formation of atherosclerotic plaques (de Lorgeril & Salen, 2004) and regulating blood pressure (Rodriguez-Leyva et al., 2010). In addition to these effects extensively discussed in the scientific literature, this essential fatty acid would be involved in the prevention of certain types of cancer (Klein et al., 2000; Shahidi & Ambigaipalan, 2018; Zheng et al., 2013) and in the improvement of conditions caused by autoimmune diseases, such as multiple sclerosis (Bjornevik et al., 2019) and arthritis rheumatoid (Nordström et al., 1995), as well as in reducing the risk of the onset of some phenomena related to inflammatory processes, such as pneumonia (Su et al., 2018).

Omega-3 fatty acids have been shown to inhibit the inflammatory process by decreasing adhesion molecule expression and inducing the production of the anti-inflammatory lipid mediators (Calder et al., 1990). They are also known to affect cytokine production (Pompos & Fritsche, 2002), secretion of chemokines (Hung et al., 2015), the production and accumulation of reactive oxygen species (ROS) (Sakai et al., 2017), and regulation of immune cell function (Fenton et al., 2013).

Cytokines are biological molecules that act as soluble mediators of natural immunity and of immune response. They constitute a group of low-molecular-weight proteins or glycoproteins produced by the cells of the immune system during the effector phase of natural and specific immunity; they mediate and control the immune response, the inflammatory reaction, and phagocytosis (Arango Duque & Descoteaux, 2014). They are currently described as multifunctional molecules, together with chemokines and adhesion molecules, which carry out important biological activities in hematopoiesis, immunity, infectious diseases, tumorigenesis, homeostasis, tissue repair, cell growth, and development (Zhang & An, 2007). In a physiological state, the levels of pro-inflammatory and anti-inflammatory cytokines in the body are kept in balance, which can be broken by abnormal activation of immune cells during viral infections. However, a dysregulated inflammatory response can cause a "cytokine storm," a clinically relevant condition that has been associated with several life-threatening diseases (Tisoncik et al., 2012). The "storm of inflammatory cytokines," in addition to chronic or acute pathological processes, is also activated by a pro-inflammatory diet, which could therefore lead to a chronic inflammatory state (Shivappa et al., 2017). Among the major players, there are processed sugars, saturated and trans fats, some additives used to enhance the flavor of foods, and the alcohol (Koebnick et al., 2018).

Chemokines and their receptors direct leukocyte recruitment in physiological and pathological conditions. Chemotactic cytokines, or chemokines, are a large subfamily of cytokines that coordinate leukocyte recruitment and activation, two crucial elements in the pathogenesis of some immune-mediated human diseases (Raman et al., 2011). The major function of chemokines is the induction of cell migration, therefore the coordination of leukocytes in pathological and physiological conditions, but they also have other biological activities, such as phagocytosis, superoxide production, release of granules, activation of phagocytes, and co-stimulation of T cells during a viral infection: They are essential mediators of inflammation and play a crucial role during infection (Melchjorsen et al., 2003). As for cytokines, the diet and in particular a diet rich in fats is able to influence the production of these molecules and their receptors (Poon et al., 2016).

The production of ROS is a physiological phenomenon, but an excess of these molecules, is able to determine a pathological state (Poljsak et al., 2013). During a viral infection, there is an increased production of ROS by phagocytes and a decrease in antioxidant enzymes which allow a greater accumulation of these at the intracellular level (Reshi et al., 2014). As for cytokines and chemokines, an imbalance in ROS levels can also be generated by an unhealthy dietary lifestyle, and at the same time, the intake of antioxidants in the diet can counteract a situation of high oxidative stress (Jiang et al., 2021).

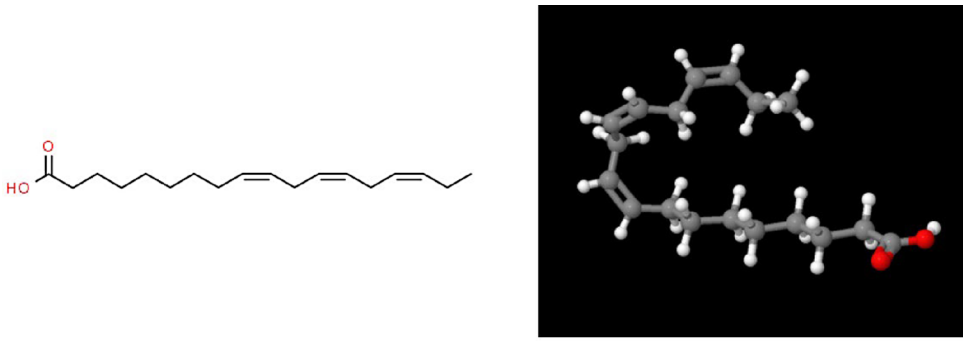

FIGURE 1 (a) 2D and (b) 3D structures of alpha-linolenic acid (ALA).

The viral infection causes of course also the involvement of different cells of the immune response (macrophages, monocytes, and neutrophils) (Knoll et al., 2021). A link between diet and the immune system has also been noted, especially in relation to the microbiome, which is closely linked with the type of followed diet. It has in fact been observed that a diet rich in fruit, vegetables, and fiber has a stimulatory and regulatory potential for the activity of immune cells (Iddir et al., 2020).

The purpose of this paper is to examine the studies carried out on the anti-inflammatory, antioxidant, and immunomodulatory capacity of ALA in different pathological or physiological situations, trying to understand its possible role in preventing a serious inflammatory and prooxidant status and a state of immune imbalance, such as the one that can occur with coronavirus disease 2019 (COVID-19), caused by the infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It will be considered those studies in which a positive activity of ALA was found against all the previously discussed situations that are also found in patients with a severe inflammatory situation due to SARS-CoV-2 infection, that is, cytokine storm, overexpression of chemokines, ROS hyperproduction, and dysregulatory effects on immune response cells. The studies evaluating a direct effect of ALA against SARS-CoV-2 are limited in number, with only one specifically focusing on its potential anti-inflammatory and immunomodulatory properties. In this study, conducted on a murine model, a substantial reduction in lung inflammation, cytokine expression, and a significant decrease in viral plaque-forming units were observed (McGill et al., 2023).

Given the limited number of direct studies available, this review has undertaken an assessment of the overall inflammatory and immunomodulatory situation that occurs during SARS-CoV-2 infection (resumed in Figure 2), and it was noted that patients affected by this disease (especially those with a severe clinical picture) have an increased serum level of several inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), different interleukins (ILs), and interferon-γ (IFN-γ) (Merad & Martin, 2020). Chemokines and their receptors play an important role during SARS-CoV-2 infection, with the function of recruiting immune response cells to the site of infection. The expression of some chemokines (CXCL10, CCL2, CCL3, CCL4, CCL5, and CXCL8) is often stimulated by cytokines (Khalil et al., 2021). Although the production of chemokines is fundamental in a first response, excessive production of these can lead to an excessive inflammatory state, high oxidative stress, impaired immune response, and the most common complication of COVID-19, acute respiratory distress syndrome (ARDS) (Merad & Martin, 2020). Free radicals and, in particular, ROS, such as peroxides, superoxides, and peroxynitrites, as well as nitric oxide, are at the basis of endothelial damage and the inflammatory state, situations that play a crucial role in the moderate and severe cases of COVID-19 infection (Otifi & Adiga, 2022). The cells of the immune response are also clearly modulated in SARS-CoV-2 infection. The first elements of the immune response that intervene following a SARS-CoV-2 infection are the B lymphocytes, responsible for the production of antibodies (Chen et al., 2022); subsequently, the T lymphocytes, the cells of the immunological memory, are involved (Moss, 2022). In the case of lymphocytes, a consistent number of patients with severe COVID-19 have been found to have an associated lymphopenia (Tavakolpour et al., 2020). It was observed that this was often associated with severe inflammation status: In several studies, it was observed that $CD4^+$ and $CD8^+$ T cell numbers were inversely proportional to inflammation markers) (Olea et al., 2022; Popescu et al., 2022). Regarding the other types of immune response cells, it has been observed that, although moderate production of macrophages contributes to the elimination of the pathogen through various inflammatory molecules, a dysregulated response, such as that which occurs in some severe cases of COVID-19, could further aggravate the clinical picture of the host causing, for example, the macrophage activation syndrome (MAS) (Merad & Martin, 2020). Also with regard to monocytes, significant changes were observed during SARS-CoV-2 infection in their size, which is increased, and in the prevalence of circulating $CD14^+$ $CD16^+$ phenotypes, which secrete a large amount of IL-6, which, as already discussed, has an important role in severe COVID-19 pulmonary syndrome (Patterson et al., 2022). Neutrophils play a fundamental role in the first immune response after a microbial infection mainly through phagocytosis mechanisms (Edirisinghe et al., 2008). It has been observed that in a severe picture of COVID-19, there is an increase in the number of these cells and an abundance of nonspecific phenotypes (Reusch et al., 2021). This situation could cause serious

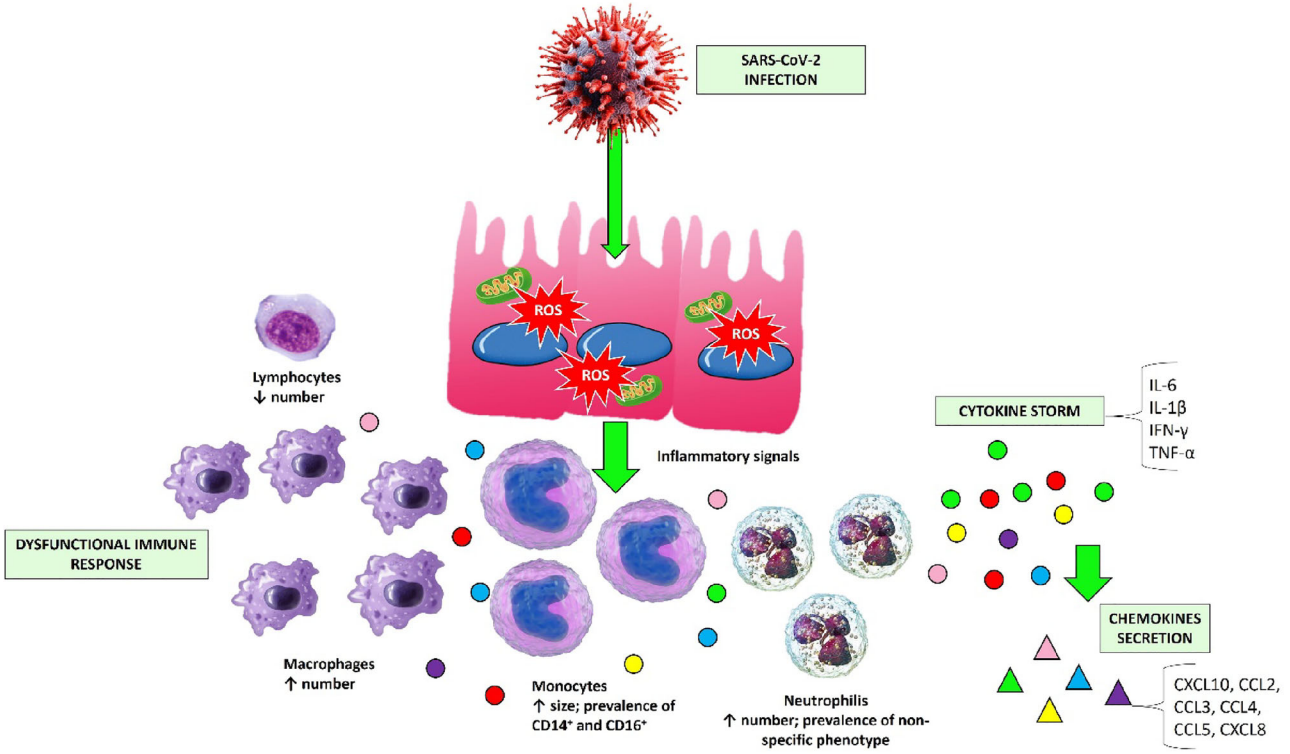

FIGURE 2 Inflammatory and immunomodulatory situation that occurs during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients affected by coronavirus disease 2019 (COVID-19) with a severe clinical picture. IL, interleukin; IFN-γ, interferon-γ; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α.

tissue damage mediated by neutrophils such as chronic obstructive pulmonary disease (COPD) and bronchiectasis in patients (Meidaninikjeh et al., 2021).

In summary, the main objective of this review is to analyze all the possible physiological and pathological non-COVID-19 situations in which ALA had a positive effect, trying to understand if this PUFA can act as a prophylactic agent for those aforementioned complications of COVID-19 that lead to serious associated pathologies and even to the death of the patient.

2 | COVID-19 AND "CYTOKINE STORM"

An hyperproduction of cytokines, called "cytokine storm," has been highlighted and widely studied in various types of viral infections caused by pathogens such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). Those viruses show phylogenetic similarities with the novel coronavirus SARS-CoV-2, the cause of the acute respiratory infection COVID-19 (Coperchini et al., 2020). Furthermore, some studies have also pointed out the inflammatory status and the "cytokine storm" in patients diagnosed with COVID-19. This overproduction of cytokines is directly correlated with lung injury, multiorgan failure, and unfavorable prognosis of severe COVID-19 (Huang et al., 2020). Cells of the innate immune system detect viral infection through germ line-encoded pattern recognition receptors (PRRs). The presence of viral sensing PRRs in multiple cellular compartments allows innate cells to recognize and immediately respond to the invading viruses (Thompson et al., 2011). The start of the inflammatory response results in the activation of signaling pathways and subsequently transcription factors, which induce the expression of genes encoding several pro-inflammatory cytokines (Ragab et al., 2020).

Three of the most important pro-inflammatory cytokines of the innate immune response, namely, ILs, TNF-α, and interferons, are the most involved in COVID-19.

In particular, there are as follows:

- **Interleukins (IL)**, a family of cytokines that mediate the immune response, in particular by regulating the acute phase of this process. A significant increase in IL-6 levels has been noted in serum of patients affected by the new coronavirus (Chen et al., 2020; McGonagle et al., 2020; Zhang et al., 2020). Furthermore, it seems that high levels of this interleukin are an element for the assessment of the severity of this respiratory disease (Henry et al., 2020), and in particular, IL-6 plays a fundamental role, it is in fact considered a biomarker of the patient's clinical profile and also a potential target for the treatment of patients (Shekhawat et al., 2021). Another important interleukin in SARS-CoV-2 infection is Il-1β, which, in addition to being correlated with the state of hyper-inflammation, would also seem to contribute to a state of hypercoagulation that could lead to micro and macrovascular thrombotic phenomena (Potere et al., 2022).

- **TNF-α** is a pro-inflammatory pleiotropic cytokine, therefore able to perform various regulatory functions in the immune response and it is also an important mediator of both acute and chronic inflammatory responses, and in turn it promotes the production of other cytokines and chemokines (Zelová & Hošek, 2013). Overproduction of this cytokine has been found in severe patients with COVID-19 and it has been observed to be closely associated with severe lymphopenia. It was assumed that targeting this molecule could improve not only the prognosis of the patient at an inflammatory level but also at an immune level (Guo et al., 2022).
- **Interferons** in general are cytokines that have a close correlation with diseases caused by viruses, such as hepatitis (Chu et al., 1995). Their role has also been found, in particular IFN-γ, in COVID-19 infection (Thijsen et al., 2020), where its hyper-production would seem equally correlated with a moderate/severe infection and therefore a poorer prognosis (Gadotti et al., 2020). Its moderate presence is necessary for the immune response to function adequately by eliminating the virus through macrophage activation, T cell differentiation, and antigen presentation. On the other hand, an exaggerated dysfunctional response can increase the secretion of other cytokines and chemokines, which upregulates the expression of ACE2 (receptor used by the new coronavirus) in epithelial cells, which would rise the replication rate of SARS-CoV-2 having consequences both for the clinical course of the disease and for the transmissibility of the virus (Heuberger et al., 2021).

3 | ALA AND INFLAMMATORY CYTOKINES

In this section, we will therefore briefly summarize those studies in which an inhibitory role of ALA has been noted in various inflammatory processes against the cytokines involved in the infection of the 2019 novel coronavirus, analyzing the in vitro, in vivo, and clinical studies written over the last 10 years (Table 1).

3.1 | In vitro studies

In C6 glial cells, where neurotoxicity with nitric oxide was induced to mimic the inflammatory state of Alzheimer's disease, the production of IL-6 and TNF-α was significantly decreased after treatment with 25 μg/mL of ALA for 2 h (Lee et al., 2018). A beneficial effect was also observed in human corneal epithelial cells, which were incubated for 2 h with ALA (125–200 μM) after lipopolysaccharide (LPS) stimulation and showed significantly lower gene expression levels of IL-6 (46.71%), IL-1β (20.86%), and TNF-α (23.81%), an effect comparable to that of corticosteroids. The inhibition was associated with a significant reduction of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα). This result highlighted the possible effect that this PUFA could have against the inflammatory state in dry eye syndrome, mediated through nuclear factor kappa light chain enhancer of activated B cells (NF-κB) signal transduction (Gadotti et al., 2020). A similar effect has been observed in the inflammatory process involving the ocular surface. In this case, the inflammation was stimulated in human conjunctival fibroblasts and in corneal epithelial cells by LPS + cytokines (IL-6, IFN-γ, TNF-α, and IL-1β): The expression of nitric oxide synthase 2 decreased by 48%–49% after treatment with ALA (200 μM) for 72 h (Erdinest et al., 2012, 2015). Also in bovine mammary epithelial cells stimulated by treatment with LPS and subsequently treated for 48 h with ALA (50 μM) the gene expression of TNF-α, IL-1β, IL-6, and IL-10 was markedly lowered (Dipasquale et al., 2018). Similarly, the production of IL-6 was observed in endothelial cells EA.hy926 (whose inflammation plays a crucial role in the initiation and progression of atherosclerosis) after stimulation with TNF-α, and it was observed that the preincubation of these cells with ALA (50 μM) for 48 h significantly decreased the levels of the cytokines mentioned in the previous study (Bork et al., 2019). In human umbilical vein endothelial cells, pretreated with LPS, the production of IL-6 after treatment with 55.6 mg/L of ALA for 24 h decreases dramatically (Shen et al., 2018), whereas in keratinocytes and in fibroblasts cultured in a 3D model tissue-engineered psoriatic skin model, the addition of 10 μM of ALA in the culture medium, downregulated the secretion of TNF-α, IFN-γ, IL-6, and IL-17A in the supernatant (Morin et al., 2022). In a cellular model (LAD 2 mast cells) in which a pseudo-allergic reaction has been induced with the Compound 48/80 (30 μg/mL) the co-treatment with different dosages of ALA (50, 100, and 200 μM) for 24 h significantly and dose-dependently reduced the secretion of TNF-α by mast cells (Ding et al., 2021). The same trend happened for IgE-mediated anaphylaxis induced with DNP–HSA (2 μg/mL) (Wang et al., 2022). An anti-inflammatory effect of ALA (at the concentration of 10 M) was also noted in rat H9c2 cardiomyocytes subjected to conditions of hyperlipidemia (with the addition of palmitic acid in the medium) and hyperglycemia (glucose): It was in fact found that the TNF-α and IL-1β significantly decreased after 24 h of treatment with this PUFA (Hajibabaie et al., 2022).

3.2 | In vivo studies

A 10-week treatment with linseed oil (rich in ALA) (40 g/kg/day) to Wistar rats, who were fed on a hypercaloric diet (which can lead to a chronic inflammatory state), exerted lower plasma concentration of TNF-α (155–130 pg/mL) and IL-6 (from 4219 to 3068 pg/mL). However, not statistically significant differences were found compared to control group (Cardoso et al., 2018). In mice with induced colitis (chronic inflammation of the colon), fed for 9 weeks on different concentrations of ALA (from 150 to 300 mg/kg/day), a significant reduction in the levels of IL-12, IL-2, IL-17A, and IFN-γ was found in the liver, even with the lowest concentration used (Wen et al., 2019). In the same line, an evident decrease in IL-6 and TNF-α levels has been observed in rats (Reifen et al., 2015). Moreover, in streptozotocin-induced diabetic rats suffering from retinopathy, the intake of ALA (75 mg/kg/day for 5 days) allowed the decrease of IL-6 levels in the retina and serum, reaching levels statistically similar to the control (Shen et al., 2013). Also in another inflammatory pathology, orchitis, induced with LPS (10 mg/kg) in albino male BALB/c mice, administration by gavage 3 days before LPS of 200 mg/kg ALA had significantly lowered serum levels of TNF-α and IL-6 (Burge et al., 2020). In male C57Bl/6 mice

TABLE 1 The effect of ALA toward cytokines in in vitro, in vivo and clinical studies.

Model	Treatment	Main results	Reference
In vitro *studies*			
C6 glial cells	25 μg/mL ALA for 2 h	↓ IL-6, TNF-α	Lee et al. (2018)
Human corneal epithelial cells (+LPS)	125–200 μM ALA for 2 h	↓ IL-6, IL-1β, TNF-α	Erdinest et al. (2012)
Human conjunctival fibroblasts/corneal epithelial cells (+LPS, IL-6, TNF-α, and IFN-γ)	200 μM ALA for 72 h	↓ NOS-2	Erdinest et al. (2015)
Bovine mammary epithelial cells (+LPS)	50 μM ALA for 48 h	↓ IL-6, IL-1β, IL-10, TNF-α	Dipasquale et al. (2018)
Endothelial cells EA.hy926 (+TNF-α)	50 μM ALA for 48 h	↓ IL-6	Bork et al. (2019)
HUVECs (+LPS)	55.6 mg/L ALA for 24 h	↓ IL-6	Shen et al. (2018)
LAD2 mast cells (+compound 48/80)	50, 100, and 200 μM ALA for 24 h	↓ TNF-α	Morin et al. (2022)
LAD2 mast cells (+DNP–HSA)	50, 100, and 200 μM ALA for 24 h	↓ TNF-α	Ding et al. (2021)
H9c2 cardiomyocytes (+palmitic acid/+glucose)	10 M ALA	↓ TNF-α, IL-1β	Wang et al. (2022)
In vivo studies			
Wistar rats (hypercaloric diet)	40 g/kg/day linseed oil (rich in ALA) for 10 weeks	↓ IL-6, TNF-α (plasma)	Cardoso et al. (2018)
Mice with induced colitis	150–300 mg/kg/day ALA for 9 weeks	↓ IL-12, IL-2, IL-17, and IFN-γ (liver)	Wen et al. (2019)
Rats with induced colitis	150–300 mg/kg/day ALA for 9 weeks	↓ IL-6, TNF-α (liver)	Reifen et al. (2015)
Streptozotocin-induced diabetic rats (with retinopathy)	75 mg/kg/day for 5 days	↓ IL-6 (retina and serum)	Shen et al. (2013)
Albino male BALB/c mice with induced orchitis (+LPS)	200 mg/kg ALA (gavage)	↓ IL-6, TNF-α (serum)	Burge et al. (2020)
Male C57B1/6 mice with type 2 diabetes (streptozotocin)+high fat/high carbohydrate diet	ALA rich diet (concentrations n.d.) for 6 weeks	↓ TNF- α (ventricular myocardium)	Russel et al. (2020)
Male C57B1/6 mice with neuronal damage induced by CdCl2	60 mg/kg/day for 6 weeks	↓ IL-1β (brain)	Alam et al. (2021)
Male C57BL/6 mice with induced acute lung injury (+LPS)	360 mg/kg ALA (intraperitoneal injection)	↓ IL-6, IL-1β, and TNF-α (BALF)	Zhu et al. (2020)
Dairy cattle	ALA rich diet (concentrations n.d.)	↓ IL-1β, TNF-α (blood mononuclear cells and milk cells)	Rezamand et al. (2016)
Male BALB/c mice with allergic rhinitis (+ovalbumin)	500 and 2000 mg/kg ALA (intragastric administration)	↓ IL-6, IL-4, and IL-1β (nasal mucosa)	Erdinest et al. (2015)
Male C57BL/6 mice with allergic rhinitis (+compound 48/80)	2 and 4 mg/kg (injection)	↓ TNF-α (serum)	Ding et al. (2021)
Male C57BL/6 mice with allergic rhinitis (+ovalbumin)	16 and 32 mg/kg ALA (injection)	↓ TNF-α (serum)	Wang et al. (2022)
CVB3 mice with myocarditis (induced by *Coxsackie virus B3*)	ALA nanoparticles (concentrations n.d.)	↓ IL-17, TNF-α (serum)	Li et al. (2021)
Clinical studies			
Healthy adults (~65 years)	14 g/day ALA for 12 weeks	↓ IL-6 (serum)	Cornish and Chilibeck (2009)
Men with dyslipidemia	15 mL/day linseed oil (rich in ALA) for 3 months	↓ IL-6 (serum)	Rallidis et al. (2003)

(Continues)

TABLE 1 (Continued)

Model	Treatment	Main results	Reference
Obese adults (40–70 years)	4.7 g/day ALA for 12 weeks	↓ TNF-α (plasma)	Joris et al. (2020)
Hypercolesterolemic subjects	19.1 g/day ALA for 6 weeks	↓ IL-6, IL-1β, and TNF-α (peripheral blood mononuclear cells)	Zhao et al. (2007)
Healthy male adults (22–44 years)	14 g/day ALA for 4 weeks	↓IL-1β and TNF-α (peripheral blood mononuclear cells)	Caughey et al. (1996)

Abbreviation: ALA, alpha-linolenic acid; BALF, bronchoalveolar lavage fluid; IL, interleukin; IFN-γ, interferon-γ; LPS, lipopolysaccharides; NOS, nitric oxide synthase-2; TNF-α, tumor necrosis factor alpha.

with type 2 diabetes induced with streptozotocin (75 mg/kg) and fed with a high-fat/high-carbohydrate diet, a subsequent ALA-rich diet of 6 weeks was observed to significantly reduce expression TNF-α in ventricular myocardium (Russel et al., 2020). In the same animal model in which neuronal damage by heavy metal exposure was induced with CdCl2 (5 mg/kg/day) and at the same time fed an ALA supplement (60 mg/kg/day) for 6 weeks, a clear decrease in protein expression of IL-1β was observed (Alam et al., 2021). The effect of ALA on acute lung injury (ALI), characterized by an uncontrolled oxidative stress and a cascade of inflammatory processes, was investigated in the same animal model. ALI was induced by intratracheal injection with LPS. The intraperitoneal injection of ALA (360 mg/kg) 1 h before LPS significantly decreased the TNF-α, IL-6, and IL-1β levels in bronchoalveolar lavage fluid (BALF). Again, the NF-κB pathway may be involved in those protective effects of ALA against inflammatory status (Zhu et al., 2020). In dairy cattle that had received an ALA-rich diet, in both blood mononuclear cells and milk cells, the gene expression of TNF-α and IL-1β decreased by about 30%–40% (Rezamand et al., 2016). In male BALB/c mice with allergic rhinitis (chronic inflammation of the nasal mucosa), induced by ovalbumin (0.5 mg) it was observed that intragastric administration of doses of 500 and 2000 mg/kg of ALA was able to decrease the gene expression of IL-1β, IL-6, and IL-4 in the nasal mucosa (Erdinest et al., 2015). Similarly, in another experimental model (C57BL/6 mice) in which an allergic pseudoreaction (passive cutaneous anaphylaxis and systemic) was induced with C48/80 (30 µg/mL), the preventive injection (30 min before) of different doses of ALA (2 and 4 mg/kg) had significantly reduced the release of TNF-α in the serum (Ding et al., 2021). Similarly, in the same experimental model with Ig-E-mediated anaphylaxis induced by ovalbumin (50 µg/mL), it was observed that the injections of 16 and 32 mg/kg of ALA were able to significantly prevent the release of TNF-α (Wang et al., 2022). In a model of viral myocarditis induced by *Coxsackie virus B3* in CVB3 mice, it has been observed that, in a dose-dependent manner, the injection of ALA nanoparticles was notably able to inhibit the production of inflammatory cytokines such as TNF-α and IL-17 (Li et al., 2021).

3.3 | Clinical studies

The clinical studies carried out to evaluate the effect of ALA on inflammation markers are few, but nevertheless, they have demonstrated a downregulatory effect of this PUFA toward cytokines. For example, in healthy adults with an average age of 65 years, who received ALA (14 g/day) as a dietary supplement for 12 weeks, a decrease in IL-6 of 36% in serum was noted (Cornish & Chilibeck, 2009). In 50 males with dyslipidemia, closely related to a state of hyperinflammation, the intake of 15 mL/day of linseed oil (rich in ALA) for 3 months significantly reduced IL-6 levels by 10.5%, whereas the intake of 15 mL/day of safflower oil (rich in linolenic acid) did not significantly affect the levels of this cytokine (Rallidis et al., 2003). Joris et al. (2020) found that 4.7 g/day of ALA taken for 12 weeks was able to decrease plasma levels of TNF-α in obese adults between 40 and 70 years. Consistent with these findings, the study conducted by Zhao et al. (2007) showed that in hypercholesterolemic subjects a diet high in ALA (providing 19.1 g ALA/day for 6 weeks) inhibited the production of IL-6, IL-1β, and TNF-α in peripheral blood mononuclear cell, compared with an average American diet. In the same line, Caughey et al. (1996) found lower mononuclear cell production of the inflammatory mediators IL-1β, TNF-α, prostaglandin E2, and thromboxane B2 in healthy subjects who consumed ALA at 14 g/day for 4 weeks. The mechanism of inhibition of cytokine production by dietary fatty acids is not completely clear, but dietary ALA appears to demonstrate anti-inflammatory effects via inhibition the NF-κB DNA-binding activity mediated by the activation of PPAR-γ (Coperchini et al., 2020).

4 | COVID-19 AND CHEMOKINES

Chemokines are low-molecular-weight proteins with chemoattracting potential, especially toward leukocytes, which play a fundamental role in recruiting cells of the immune system during inflammatory processes. To date, about 50 different types of chemokines are known and about 20 receptors of these which are divided into different families (CX3C, CXC, CC, and C), based on their chemical structure (Hughes & Nibbs, 2018).

In the scientific literature, a role of this class of molecules in viral infections has been recognized; these would seem to act as a sort of obstacle for the entry of viral particles as well as subsequently inhibit proliferation, regulate apoptosis and, as previously mentioned, modulate the immune response. Among several cytokines, the ones most involved in viral infections, especially at the respiratory level, seem to be CXCL10 and CXCL8 (Dong et al., 2021). Usually, following a viral infection, the chemokines in circulation increase to

counteract the disease, but it can also happen that the virus interferes with the cytokine/receptor system in its favor to modify the different intracellular pathways by increasing the viral replication rate (Alcami, 2016).

Specifically, about SARS-CoV-2 infection, there are not many studies, but to try to understand the various dynamics, the infections from SARS-CoV and MERS-CoV are observed (Liu et al., 2021). For what concern SARS-CoV, in infected patients it was noted that during the infection the number of circulating chemokines was significantly increased, especially the serum levels of CXCL10, CXCL8, CCL2, and receptors CCR4 and CCR7 (Khalil et al., 2021). It has been observed in several studies that a disproportionate presence of cytokines during the infection could lead to dysregulation of the IFN-β (such as a late activation or a low production of this) (Hadjadj et al., 2020). This dysfunction could therefore contribute to increasing the efficiency of the immune evasion mechanism of the virus with consequent worsening of the patient's health status. Also with regard to MERS-CoV infection, similarly, an increase in serum levels in particular of two cytokines has been observed in several studies: CXCL10 and CXCL8 with a parallel decrease in the levels of IFNs (Bello-Perez et al., 2022; Channappanavar et al., 2019; Kesmez Can et al., 2021). As mentioned earlier, data regarding SARS-CoV-2 are scarce, but it has been observed that it is capable of upregulating some chemokines, such as CXCL10, CCL8, CCL2, CXCL1, and CXCL5 (Bohnacker et al., 2022; Gudowska-Sawczuk & Mroczko, 2022; Hsu et al., 2022). The effect on IFNs in this case is not clear since some studies have found an increase, whereas others a decrease (Kim & Shin, 2021; Lee et al., 2018).

5 | ALA AND CHEMOKINES

In this section, it will be collected the in vitro, in vivo, and clinical studies in which it was observed that ALA was able to modulate the levels of chemokines and its receptors, to try to add information about the possible effect that this PUFA could have in the increase of these molecules that also occurs in moderate/severe infection with the new coronavirus SARS-CoV-2. Most of the studies in the literature concern the effect of ALA on chemokine CXCL8 (IL-8) (Table 2).

5.1 | In vitro studies

In keratinocytes and fibroblasts in a 3D tissue-engineered psoriatic skin model, the addition in the culture medium of 10 μM of ALA (for 3 weeks) downregulated chemokine levels, such as CXCL1, IL-8, CXCL10, CCL2, and CCL5, also called regulated on activation, normal T cell expressed, and secreted (RANTES) (Morin et al., 2022). There are several inflammatory disorders affecting the ocular surface and that can have serious consequences for sight. In a cellular model of human corneal epithelial cells in which inflammation was stimulated by LPS (1000 ng/mL), a 2 h preincubation of the cells with ALA (125–200 μM) significantly decreased the gene expression levels of IL-8 (52.21%). It has been speculated by the authors that this decrease was likely associated with a downregulation of I-κBα (Erdinest et al., 2015). In human endothelial cells hyperstimulated for 24 h with TNF-α (1 ng/mL), treatment with 100 μM of ALA for 48 h clearly lowered the levels of two chemokines really important in a state of hyper-inflammation, especially following a viral infection, which are RANTES e IL-8 (Bork et al., 2019). Similar results in the same cell model were obtained with lower concentrations (10, 25, and 50 μM) in a non-dose-dependent manner (Baker et al., 2020).

Among the major risk factors of inflammatory gastrointestinal pathological conditions (gastritis, ulcers, and even some adenocarcinomas) there is the presence of *Helicobacter pylorii*. Infection by this bacterium is mediated by the activation of neutrophils, which in turn is regulated by the cytokine CXCL8. Human gastric epithelial cells pretreated with 20, 50, and 100 μM of ALA for 24 h and subsequently placed in contact with *H. pylorii* for 4 h have shown a gene and protein expression of CXCL8 significantly lower than untreated cells with a dose-dependent trend (Lee et al., 2014). In a cellular model (LAD 2 mast cells) in which a pseudo-allergic reaction was induced with the Compound 48/80 (30 μg/mL) was observed that a co-treatment with different dosages (50, 100, and 200 μM) of ALA significantly and dose-dependently reduced secretion of CCL-2 and IL-8 (Ding et al., 2021). On the same cell line in which IgE-mediated anaphylax was induced by sensitizing the cells with a 12 h treatment with DNP-IgE (2 μg/mL), it was observed that the 30-min treatment with ALA (50, 100, and 200 μM) reduced mast cell degranulation and release of chemokines such as CCL2 and IL-8 in a dose-dependent manner (Wang et al., 2022).

5.2 | In vivo studies

A diet enriched with 3%, 6%, and 9% of ALA in dairy cattle led to a significant reduction (~20%) of the expression of IL-8 in the peripheral blood mononuclear cells of animals (Rezamand et al., 2016). Similarly, in lambs previously infected with *Coxsakievirus A* (which causes hand and mouth disease) and fed with an ALA supplement (doses n.d.), a lower expression of IL-8 mRNA at tissue level was demonstrated (Adibnia et al., 2022). Juvenile grass carps fed with a diet rich in ALA for 60 days showed a much lower gene expression of IL-8 in the intestinal segments than in animals fed with classic feed (Zeng et al., 2016). Always in carps supplemented with ALA in the same way, but to which an inflammatory response by LPS of *Escherichia coli* (100 μg) was induced after 42 days of feeding, a significant reduction of IL-8 and CXC gene expression was observed in the renal tissue of the head (Nguyen et al., 2022). In C57BL/6 mice in which an allergic pseudoreaction (passive cutaneous anaphylaxis and systemic) was induced with C48/80 (30 μg/mL), the preventive injection (30 min before) of different doses of ALA (2 and 4 mg/kg) significantly reduced IL-8 and CCL2 release in animal serum (Ding et al., 2021). Similarly, in the same experimental model with ovalbumin-induced Ig-E-mediated anaphylaxis (50 μg/mL), it was observed that the injection of 16 and 32 mg/kg of ALA significantly prevented the release of the same previous chemokines and in a dose-dependent manner (Wang et al., 2022).

TABLE 2 The effect of ALA toward chemokines in in vitro, in vivo, and clinical studies.

Model	Treatment	Main results	Reference
In vitro studies			
Keratinocytes and fibroblast (3D tissue-engineered model)	10 μM ALA for 3 weeks	↓ CXCL1, IL-8, CXCL10, CCL2, RANTES	Morin et al. (2022)
Human corneal epithelial cells (+LPS)	125–200 μM ALA for 2 h	↓ IL-8	Erdinest et al. (2012)
Human endothelial cells (+TNF-α)	100 μM ALA for 48 h	↓ IL-8 and RANTES	Bork et al. (2019)
Human endothelial cells (+TNF-α)	10, 25, and 50 μM ALA for 48 h	↓ IL-8 and RANTES	Baker et al. (2020)
Human gastric epithelial cells (+*Helicobacter pylorii*)	20, 50, and 100 μM ALA for 24 h	↓ IL-8	Lee et al. (2014)
LAD2 mast cells (+Compound 48/80)	50, 100, and 200 μM ALA for 24 h	↓ IL-8 and CCL2	Ding et al. (2021)
LAD2 mast cells (+DNP-IgE)	50, 100, and 200 μM ALA for 30 min	↓ IL-8, CCL2 ↓ mast cells degranulation	Wang et al. (2022)
In vivo studies			
Dairy cattle	Diet enriched with 3%, 6%, 9% ALA	↓ IL-8 (peripheral blood mononuclear cells)	Rezamand et al. (2016)
Lamb infected with *Coxsakievirus A*	Diet with ALA supplement (concentration n.d.)	↓ IL-8 (tissue)	Adibnia et al. (2022)
Juvenile grass carps	Diet rich in ALA (concentration n.d.) for 60 days	↓ IL-8 (intestinal segments)	Zeng et al. (2016)
Carps (+LPS)	Diet rich in ALA (concentration n.d.) for 42 days	↓ IL-8 and CXC (renal tissue of the head)	Nguyen et al. (2022)
Male C57BL/6 mice with allergic rhinitis (+compound 48/80)	2 and 4 mg/kg (injection)	↓ IL-8 and CCL2	Ding et al. (2021)
Male C57BL/6 mice with allergic rhinitis (+ovalbumin)	16 and 32 mg/kg ALA (injection)	↓ IL-8 and CCL2	Wang et al. (2022)
Clinical studies			
Healthy volunteers (ex vivo stimulation on whole blood with LPS)	240 mg/day ALA for 2 weeks	↓ IL-8	Schubert et al. (2007)
Stable patients with COPD	Diet rich in ALA (concentration n.d.)	↓ IL-8	Meidaninikjeh et al. (2021)

Abbreviation: ALA, alpha-linolenic acid; CXCL, chemokine (C-X-C motif) ligand; CCL, chemokine ligand; DNP, 2,4-dinitrophenol; IL, interleukin; Ig, Immunoglobulin; LPS, lipopolysaccharides; RANTES, regulated on activation, normal T cell expressed, and secreted; TNF-α, tumor necrosis factor alpha.

5.3 | Clinical studies

Few clinical studies have actually observed a direct effect of the PUFA in question on chemokines, probably because in several studies it has been evaluated the effect at systemic level (blood tests) (de Batlle et al., 2012; Warstedt et al., 2009), and it is instead more probable that an effect is found at a local level since, for example, IL-8 is a powerful chemoattractant that recruits and activates neutrophils (Tanino et al., 2002).

In healthy volunteers who received a diet supplemented with 240 mg/day of ALA for 2 weeks, it was observed that, after ex vivo stimulation with *E. coli* LPS on whole blood to simulate an inflammatory response, the release of IL-8 was lower when compared to the control group both at the end of the supplementation and 2 weeks after the end of it. COPD is a serious inflammatory situation that is often chronic and occurs concurrently with some diseases (including COVID-19) or as a consequence of exposure to certain chemical/physical agents (Schubert et al., 2007). It was observed that in stable patients who followed a diet rich in ALA (concentration n.d.), the amount of IL-8 in the serum was less than in the control group (Meidaninikjeh et al., 2021).

6 | COVID-19 AND OXIDATIVE STRESS

As already mentioned in the introduction of this manuscript, inflammation but also oxidative stress are key factors during SARS-CoV-2 infection. In fact, they are considered to be fundamental, almost essential from the point of view of the immune response in a pathophysiological situation such as a viral infection, but which, if too unbalanced, can lead to a worsening of the patient's clinical picture (Forcados et al., 2021). There are not many studies regarding the role of ROS, specifically in COVID-19 pathology. It is known that an

TABLE 3 The effect of ALA toward oxidative stress in in vitro, in vivo, and clinical studies.

Model	Treatment	Main results	Reference
In vitro studies			
Wild boar sperm cells	3 ng/mL ALA in freezing liquid	↓ ROS	Lee et al. (2019)
Endothelial cells (+chlorambucil)	15 ng/mL ALA for 24 h	↓ 8-isoprostane nitrotyrosine	Ambrozova et al. (2010)
Murine macrophages RAW 264.7 (+LPS)	100 μM ALA for 8 h and 20 h	↓ ROS and RNS	Monaco et al. (2018)
SH-SY5Y human neuroblastoma cells (+Aβ25−35)	5–25 μM ALA for 24 h	↓ ROS	Lee et al. (2018)
In vivo studies			
C57BL/6N mice (+Cd_2Cl_2)	60 mg/kg/day ALA for 6 weeks	↓ ROS (intracellular level)	Alam et al. (2021)
Obese Zucker rats	Diet supplemented with +10% flaxseed oil (rich in ALA) for 4 weeks	↓ ROS (mitochondrial level)	Monaco et al. (2018)
Clinical studies			
Patients with hypercholesterolemia	Diet supplemented with +8.6 wheat germ oil (rich in ALA) for 2 months	↓8-hydroxy-2′-deoxyguanosine ↓CD40L	Alessandri et al. (2006)
Obese subjects (18–60 years)	1200 mg/day ALA for 8 weeks	↓ Ox-LDL, 8-iso-PGF2 (blood)	Yan et al. (2013)
Patients with polycystic ovary syndrome	400 mg/day ALA + 400 IU/day vitamin E for 12 weeks	↓ ROS, Ox-LDL, malondialdehyde (peripheral blood)	Rahmani et al. (2017)

Abbreviation: Aβ, Amyloid beta-peptide; ALA, Alpha-linolenic acid; CD40L, cluster of differentiation 40 protein ligand; LPS, lipopolysaccharides; Ox-LDL, oxidized low-density lipoprotein; PGF2, prostaglandin F2; ROS, reactive oxygen species; RNS, reactive nitrogen species.

excessive situation of oxidative stress could promote phenomena such as inflammation, tissue damage, and increase cellular apoptotic rate that lead to serious consequences observed in some patients with severe COVID-19, such as multi-organ failure, pulmonary edema, thrombus formation, ARDS, and ultimately death (Aslan et al., 2021; Paidas et al., 2022; Semeraro & Colucci, 2021).

7 | ALA AND OXIDATIVE STRESS

In this section, it will be collected the in vitro, in vivo, and clinical studies in which it was observed that ALA was able to modulate an excessive situation of oxidative stress, in particular the intracellular accumulation of ROS in different pathological and physiological situations (Table 3). As the studies are numerically scarce, they will all be discussed in the same paragraph.

In wild boar sperm cells, it has been observed that 3 ng/mL of ALA supplemented in freezing liquid decreased the production of ROS when thawed and with lipid peroxidation induced (Lee et al., 2019). Steinritz et al. (2014) observed that 24 h treatment with ALA (15 ng/mL) of early endothelial cells previously stressed with chlorambucil (12.5 μg/mL) for 24 h (alkylating agent, and an active ingredient used in various dermatological and tumor diseases that causes several side effects) was able to significantly decrease the levels of 8-isoprostane and nitrotyrosine, two biomarkers indicating the levels of ROS and RNS. Macrophages RAW 264.7 with induced situation of oxidative stress through pretreatment with bacterial endotoxin LPS at a concentration of 0.1 μg/mL when post-treated with ALA concentrations of 100 μM showed significantly lower levels of ROS (after 8 h of treatment) and RNS (after 20 h of treatment) (Ambrozova et al., 2010). Alzheimer's disease is characterized by an abnormal accumulation of amyloid plaques that increase the production of ROS by stimulating apoptotic phenomena at the neuronal level. To investigate whether ALA had any neuroprotective effect on this phenomenon, SH-SY5Y human neuroblastoma cells were induced with Aβ25–35 (25 μM) for 2 h and co-treated with ALA (5–25 μM) for 24 h. A marked percentage decrease in ROS levels was observed in cells that had been treated with the C18:3 $\omega-3$ (Lee et al., 2018). To investigate the neuroprotective effect of ALA, Alam et al. (2021) induced neuronal damage from exposure to heavy metals in male C57BL/6N mice with CdCl2 (5 mg/kg/day), and at the same time they fed them with a supplement of ALA (60 mg/kg/day) for 6 weeks. The accumulation of ROS at the intracellular level in the group that received ALA was significantly decreased. In obese Zucker rats who had received a diet supplemented by ALA (+10% flaxseed oil) for 4 weeks and divided into two groups: sedentary and subjected to physical activity, the accumulation of ROS at the mitochondrial level was observed to significantly decrease but only in the sedentary group (Monaco et al., 2018). It has been hypothesized in several studies that the PUFA in question has a protective effect against different pathologies with an atherosclerotic basis, probably counteracting the oxidative stress caused by an upregulation of the CD40 ligand (L). In a study conducted by Alessandri et al. oxidative stress levels (8-OHdG) and CD40L expression were measured in patients with hypercholesterolemia who had received a diet supplemented by ALA (+8.6% wheat germ oil) for 2 months. A clear decrease in the oxidative biomarker 8-OHdG and in the expression of CD40L was noted in the patients with supplemented diet compared to those who had not received C18:3 $\omega-3$ as a source of vegetable oil in the diet (Alessandri et al., 2006). Even for those pathologies related to a state of severe obesity, oxidative stress plays a fundamental role, especially in the onset of the various CVDs.

In obese people (18–60-year old), ALA supplementation (1200 mg/day) for 8 week was able to lower some biomarkers of oxidative stress, such as the levels of Ox-LDL and 8-iso-PGF2a in the blood, compared to the placebo group (Yan et al., 2013). An improvement of a prooxidant situation was also observed in patients with polycystic ovary syndrome, a disease closely associated with increased ROS production. The patients received 400 mg of ALA + 400 IU of vitamin E per day as a dietary supplement for 12 weeks. At the end of the interventional diet, a net decrease in some markers of oxidative stress was found in the peripheral blood of women who had taken ALA such as Ox-LDL mRNA and levels of malondialdehyde (Rahmani et al., 2017).

8 | COVID-19 AND IMMUNE RESPONSE CELLS

As can be easily intuitable, the cells of the immune response in SARS-CoV-2 infection are largely modulated. However, if this response is normally mediated in those patients who do not develop a severe clinical picture, it is strongly dysregulated in the most severe situations, and this can lead to the development of further damage and real syndromes, such as lymphopenia, MAS, COPD, and bronchiectasis, which seriously and further aggravate the patient's prognosis (Dhaliwal et al., 2022; Martinez-Garcia et al., 2021; McGonagle et al., 2021; Southworth et al., 2022). As mentioned in the introduction, the first immune response cells that are involved in SARS-CoV-2 infection are lymphocytes: first the B, which are responsible for the primary production of antibodies, and then the T ones, which intervene in the formation of the immunological memory (Kwiecień et al., 2020). It has been observed that in severe cases, a situation of lymphopenia that aggravates the clinical picture of the patient is frequent, and that this is often strongly and significantly associated with an evident pro-inflammatory status. In fact, studies have been carried out in which in hospitalized patients, an inversely proportional relationship was found between different markers of inflammation and the number of $CD4^+$ and $CD8^+$ T-cells (Ghizlane et al., 2021; Olea et al., 2022; Popescu et al., 2022). Several clinical studies have also shown that lymphopenia is an important prognostic factor in the case of COVID-19. Trying to understand the mechanisms behind this lymphopenia situation in patients with SARS-CoV-2 infection is of primary importance. As seen before, this situation is related to an increase in pro-inflammatory markers; according to one recent study carried out, it could be the massive presence of pro-inflammatory cytokines that are present during the "cytokine storm" that leads to a massive apoptotic phenomenon of lymphocytes (levels of IL-6 and Fas–FasL interaction) (Mazzoni et al., 2020). It could be important to evaluate a supportive therapy that in these patients can counteract this situation of lymphopenia favoring a positive course of the disease. As for the macrophages, in case of infection, they recognize the microorganism through the so-called PRRs and activate a whole series of pro-inflammatory patterns and participate in the recruitment of other effector cells of the immune response (Xie et al., 2021). In severe cases of COVID-19, however, a dysregulated response has been observed which can further aggravate the clinical picture of the host. An example of this harmful response is in MAS, which is characterized by the exaggerated activation of macrophages that secrete high amounts of cytokines. This syndrome can in fact be described as a state of systemic hyperinflammation that is often observed in patients with different serious pathologies (Otsuka & Seino, 2020). This "cytokine storm" that derives from it, if not countered, results in serious tissue damage. The cytokines particularly involved in this syndrome are TNF-α, IL-6, and IL-1β (Ombrello & Schulert, 2021).

In addition to tissue damage, it has been observed that these cytokines could also contribute to the activation of the coagulation cascade by increasing the production of plasminogen activator inhibitors, thus contributing to the occurrence of thrombosis cases in patients with severe COVID-19 syndrome (Esposito et al., 2021). There are two main subtypes of macrophages: M1, which is the "classically" activated macrophage with pro-inflammatory function and which produces TNF-α, IL-1β, IL-6, and chemokines such as CCL8 as well as ROS, and the other phenotype is M2, the "alternatively" activated anti-inflammatory macrophage, which, in response, secretes anti-inflammatory cytokines such as IL-4 and IL-10 to counteract the excessive cytokine storm (Kosyreva et al., 2021). Usually, in normal pathological conditions, the ratio between M1/M2 is shifted toward the second phenotype, while it is observed that in severe cases of COVID-19 with associated ARDS, the relationship between the M1 and M2 phenotypes is completely unbalanced in favor of the first. The M1 phenotype is in fact responsible for the release of those pro-inflammatory cytokines that favor the establishment of MAS (Ahmad et al., 2022; Lian et al., 2022).

Monocytes, in response to the entry of the microorganism, reach the site of infection and begin the phenomena of phagocytosis. Even monocytes during SARS-CoV-2 infection undergo dysregulations (especially in patients with more severe clinical pictures). In patients who required hospitalization, alterations were found both in their size and in the more massive presence of some phenotypes (called inflammatory phenotypes) ($CD14^+$ and $CD16^+$) instead of others that produce higher amounts of IL-6, IL-10, and TNF-α, thus leading to a further aggravation of the pro-inflammatory situation that is already present in patients with severe COVID-19. There are no studies that have found a significant change in the number of monocytes during COVID-19 disease, or at least there is no stable trend as studies have been done, but in some of these the number appears to have increased and in others decreased (Rajamanickam et al., 2021; Utrero-Rico et al., 2021). Instead, there are several studies that note a change in the size of these, which appear to be larger, especially in patients requiring hospitalization (Kubánková et al., 2021).

Generally after a bacterial/viral infection, neutrophils migrate from the bloodstream into the tissue site of infection and contribute to the elimination of the pathogen through phagocytosis or with the release of neutrophil extracellular traps (NETs) and of pyrogenic and pro-inflammatory molecules (Kaplan & Radic, 2012).

It has been observed, as in other serious diseases (inflammatory and immune disorders, sepsis, cancer, and severe cardiovascular diseases), that the neutrophil to lymphocyte ratio is a prognostic record for the prognosis of the different diseases (Afari & Bhat, 2016; Grassadonia et al., 2021; Liu et al., 2016). It has also been shown that the number of neutrophils present in peripheral blood samples from patients

with a severe clinical picture is significantly higher than in patients with a normal course of the disease (Toori et al., 2021). A correlation was then found between the number of circulating neutrophils and the development of pulmonary infiltrations and thrombosis (Fu et al., 2020).

As mentioned previously, neutrophils to counteract the infection produce molecules called NETs, which are structures formed mainly by chromatin that serve to "trap" the pathogenic microorganisms, causing the so-called NETosis, which although it is a defense process against infections, if hyperactivated and in certain conditions it can damage the tissues (Cahilog et al., 2020). Recent studies have been performed and they reveal that COVID-19 patients with severe clinical picture have an elevation of typical NETosis markers (lactate dehydrogenase, citrullinated histone H3, MPO–DNA complexes, and cell-free DNA) (Monaco et al., 2022). This state of NETosis is correlated with the development of the "cytokine storm," release of ROS which as a consequence, leads to ARDS and contributes to microvascular thrombosis phenomena (Barnes et al., 2020). In addition to an increased number of neutrophils proven during SARS-CoV-2 infection, a greater number of immature neutrophils were found, probably correlated with the hyperinflammatory status and in particular with the massive presence of the cytokine IL-6 and chemokine CXCL10 (both probably regulated by IL-17) (Rice et al., 2022). Different studies have been performed that have correlated the increased ratio of immature versus mature neutrophils to a greater severity of the disease, explained by the fact that increasing inflammation drives neutrophils into the lungs and consequently stimulates a higher release of immature neutrophils from the bone marrow (Carissimo et al., 2020). Often these dysregulations affecting neutrophils are directly correlated with the onset of two comorbidities that further worsen the clinical picture of patients with severe COVID-19 which are COPD (Olloquequi, 2020) and bronchiectasis (Reusch et al., 2021). Another aspect to consider, which in addition to neutrophils also concerns monocytes is the more consistent presence in patients with severe COVID-19 of platelet aggregates called "Neutrophil-Platelet aggregates (NPA) and Monocyte-Platelet Aggregates (MPA)" which were found to be correlated with higher inflammatory status and disease severity (Le Joncour et al., 2020).

All these aspects and numerical, phenotypic, morphological modifications of the different immune response cells taken into consideration during SARS-CoV-2 infection deserve to be studied in more detail. In fact, they could both become biomarkers of patient prognosis and be new targets for different therapeutic approaches aimed at improving the clinical picture, especially in those patients with severe pathology.

9 | ALA AND IMMUNE RESPONSE CELLS

In this paragraph, it will be discuss the in vitro, in vivo, and clinical studies in which it was observed that ALA was able to inhibit or, improve all those functional, quantitative, and morphological dysregulations affecting the immune response cells described in the previous paragraph in different pathological and physiological situations to try to enrich the literature and try to understand if there could be a direct effect in COVID-19 pathology (Table 4).

10 | IN VITRO STUDIES

As previously mentioned, the M1 macrophage phenotype produces a higher amount of cytokines; in a significant study it was observed that in M1-like macrophages (THP-human monocytes activated with 20 ng/mL of IFNγ + 10 pg/mL of LPS), pre-differentiation treatment with 60 μM of ALA significantly decreased cytokine secretion, such as IL-1β, TNF-α, and IL-6 (Pauls et al., 2018). Similarly, THP-human monocytes stimulated to differentiate into an M2a-like macrophage phenotype (with the use of IL-4 and IL-13) with the presence in the differentiation medium of 60 μM of ALA show a greater capacity of phagocytosis. Furthermore, in the same study it was observed that the presence of the PUFA in question in the medium of differentiated M2-like macrophages significantly and in a dose-dependent manner (0.5–25 pg/mL) decreases the secretion of the pro-inflammatory chemokine CCL-2 (Pauls et al., 2020). Human monocytic THP-1 cells were pretreated with a wide range of ALA concentrations (0.5–100 μM) for 2 h and subsequently stimulated with LPS (1 μg/mL) for 24 h. Both the amount of cytokines secreted in the medium and the gene expression of the same (IL-6, IL-1β, and TNF-α) were then measured and in both cases there was a clear dose-dependent decrease (Zhao et al., 2005).

10.1 | In vivo and clinical studies

An interesting study on the immunomodulatory activity of ALA was carried out on groups of male Wistar rats, both carriers and noncarriers of Walker 256 tumor, fed for 4 weeks with diets not supplemented or supplemented with fish oil or oil rich in ALA (47%–51%). It was observed that in both groups (carriers or not) that had received the oil rich in ALA, compared to the others there was a greater phagocytic capacity of the immune cells (stimulated ex vivo with 100 μg of LPS) and an increased elimination of antigens. Furthermore, a decrease in the secretion of pro-inflammatory cytokines (IL-6 and TNF-α) by macrophages has been demonstrated (Schiessel et al., 2016).

Type 2 diabetes mellitus is often associated with a state of chronic inflammation, which is also a contributing cause; a co-adjuvant anti-inflammatory therapy could therefore lead to improvements in some complications associated with it, such as vasculopathies, retinopathies, nephropathy, and neuropathies. In this context, Sprague–Dawley rats with induced type 2 diabetes mellitus with intraperitoneal administration of streptozotocin–nicotinamine were supplemented with dietary ALA (10%) for 5 weeks. It was observed that the number of infiltrated macrophages in the liver of rats fed with ALA supplementation was significantly lower than in those who did not receive it. Furthermore, it has been shown that ALA supplementation favors the polarization of macrophages toward the M2 phenotype rather than toward M1. In fact, there is a clear decrease in some pro-inflammatory

TABLE 4 The effect of ALA toward immune response cells in in vitro, in vivo, and clinical studies.

Model	Treatment	Main results	Reference
In vitro studies			
THP-human monocytes (+IFN-γ, +LPS)	60 μM ALA for 2 h	↓ IL-1β, IL-6, and TNF-α	Pauls et al. (2018)
THP-human monocytes (+IL-4 and IL-13)	60 μM ALA for 2 h	↑ Phagocytosis activity ↓ CCL-2	Pauls et al. (2020)
THP-human monocytes (+LPS)	0.5–100 μM ALA for 2 h	↓ IL-1β, IL-6, and TNF-α	Zhao et al. (2005)
Murine macrophages RAW 264.7 (+LPS)	20 μM ALA for 2 h	↓ IL-1β, IL-6, IL-18, and TNF-α ↑ Polarization versus M2 phenotype ↑ Arg1 ↑ IL-10	Liu et al. (2022)
In vivo studies			
Male Wistar rats (Walker 256 tumor) (ex vivo stimulation with LPS)	Oil rich in ALA (47%–51%) for 4 weeks	↑ Phagocytosis activity ↑ Elimination of antigens ↓ IL-6, TNF-α	Schiessel et al. (2016)
Sprague–Dawley rats with type 2 diabetes mellitus (+streptozotocin–nicotinamine)	Diet rich in ALA (10%) for 5 weeks	↑ Polarization versus M2 phenotype ↓ IL-6, IL-1β, IL-17A, and TNF-α	Liu et al. (2022)
Male C57BL mice	1 g/kg/day ALA for 3 days (intragastric administration)	↑ Polarization versus M2 phenotype ↑ Arg1	Ohue-Kitano et al. (2018)
Pregnant goats (*Ettawa grade*)	Diet with ALA supplementation (2.8%) (from 4th-month gestation until 2 weeks after parturition)	↓ Size of monocytes ↓ Number of neutrophilis ↓ ROS production	Nugroho et al. (2020)
Male mice homozygous for HbS (+LPS ex vivo)	Diet rich in ALA (7.3%) for 4 weeks	↓ NPA formation ↓ Neutrophil activation	Stivala et al. (2022)
C57BL/6 mice (+LPS)	ALA (intraperitoneal injection)	↓ Infiltrated neutrophilis (BALF) ↓ Minor damage to the tissue-lung ↓ IL-6, IL-1β, and TNF-α	Zhu et al. (2020)
Clinical studies			
Women (20–51 years) with high BMI (30–51 kg/m^2)	4 g/day ALA for 4 weeks	↓ Number of monocytes with pro-inflammatory phenotype	Pauls et al. (2021)

Abbreviation: ALA, alpha-linolenic acid; Arg1, arginase 1; CCL, chemokine ligand; HbS, hemoglobin S; IFN-γ, interferon-gamma; IL, interleukin; LPS, lipopolysaccharides; NPA, neutrophil-platelet aggregate; ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha.

cytokines in plasma, such as IL-1β, IL-6, IL-17A, and TNF-α (Liu et al., 2022). Male C57BL mice received intragastric administration of ALA of 1 g/kg/day for 3 days, and subsequently, mouse bone marrow-derived cells (BMDCs) from femurs and tibias were extracted: Expression of the Arg1 gene was investigated in these cells, marker of polarization toward an M2 macrophage phenotype and it was observed that the gene expression of this was much higher in BMDCs from mice that received the administration of ALA (Ohue-Kitano et al., 2018). In goats (Ettawa grade) a diet with supplementation of 2.8% ALA was provided from 4-month gestation until 2 weeks after parturition: In these a reduced size of monocytes, a lower number of neutrophils were noted in the blood as well as a reduced production of ROS (Nugroho et al., 2020). As previously mentioned, the presence of NPA in COVID-19 patients is an aggravating factor. Stivala et al. (2022) observed that male mice homozygous for HbS fed with a diet rich in ALA (7.3%) for 4 weeks showed reduced NPA formation and decreased neutrophil activation ex vivo following LPS stimulation compared to mice that received a diet low in ALA (0.03%). ARDS is one of the main complications and causes of mortality in patients with COVID-19 and as previously mentioned it is characterized by an unbalanced state of oxidative stress and severe inflammatory processes that lead to major cell and tissue damage. This syndrome was induced in C57BL/6 mice with the inoculation of 25 μg of LPS intratracheally to which ALA had been or was not previously administered (1 h before) with intraperitoneal injection. It was observed that mice that had received pretreatment with ALA in addition to a minor damage to the tissue-lung level, in the BALF had a lower number of infiltrated neutrophils and a lower secretion of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β (Zhu et al., 2020).

As mentioned several times in this manuscript, inflammation is a situation closely associated with the condition of obesity. In the only clinical study in the literature, it was observed that the consumption of 4 g/day of ALA in women (20–51 years) with high BMI (30–51 kg/m2) for 4 weeks was able to reduce the number of monocytes with pro-inflammatory phenotype (Pauls et al., 2021).

11 | DISCUSSION

At this point, we repurpose the question asked previously: can a balanced diet supplemented by foods and/or compounds (like ALA), that has a proved effect on cytokines and chemokines and also plays an

important role in preventing/improving oxidative stress and in immune response, help to improve the patient's prognosis and/or alleviate the degree of severity in SARS-CoV-2 infection?

In general, it can be said that a state of chronic inflammation, oxidative stress, and immune system dysfunctions due to an unhealthy lifestyle or different pathologies could lead to a more serious disease course in different pathologies (Hamer et al., 2020; Peyneau et al., 2022; Stockley, 2009; Sharifi-Rad et al., 2020). The role of diet in the current global pandemic is a reason for study. It is important to understand whether a balanced diet, rich in foods/compounds with a proven anti-inflammatory, antioxidant, and immunomodulatory activity, can prevent the onset of this disease or alleviate the symptoms, especially those caused by the "cytokine storm." Some studies in recent months have tried to evaluate if the supplementation of certain compounds in the diet can help to protect against SARS-CoV-2 infection. Among the various compounds, particular attention was paid to vitamin D, which seems to have a protective role against respiratory tract infections, even if no evidence was found regarding the reductive effect on the severity of COVID-19 (Ali, 2020; Aygun, 2020; Cheng, 2020; Grant et al., 2020). Regarding inflammation and pro-inflammatory markers, vitamin D significantly reduced the levels of IL-6 and C-reactive protein, which were increased in patients with COVID-19, without any side effects (Lakkireddy et al., 2021). Other studies were carried out assuming a synergistic effect of this vitamin with other compounds, such as melatonin (Martín Giménez et al., 2020), ascorbic acid, zinc, and *N*-acetylcysteine (Bauer et al., 2020). Vitamin C was also considered a potential helper to decrease the duration of viral SARS-CoV-19 infection (Hemilä & Chalker, 2020), assuming a possible synergistic effect with quercetin which has a proven antiviral effect (Colunga Biancatelli et al., 2020). Other bioactive compounds with strong and proven anti-inflammatory and antioxidant activity are polyphenols (Battino et al., 2021). For example, among these phenolic compounds, curcumin has been taken into consideration in recent months, for its proven effects in inhibiting the entry of different viruses into the cells and in modulating different viral pathways (Zahedipour et al., 2020). Resveratrol was considered for its high antioxidant and anti-inflammatory activity as well as the antiviral action against several viruses (Marinella, 2020).

Reduced macrominerals and trace elements have been associated with increased risk of infection. For instance, magnesium intake has been inversely associated with the concentrations of hs-CRP, IL-6, and TNF-α in a dose-dependent manner (Chacko et al., 2010). Carotenoids concentration have also received attentions for their potential antiviral role because they impact immune functions by regulating membrane fluidity, and some of them are precursors for vitamin A and exert immune-modulating functions attributed directly to vitamin A status (Chew & Park, 2004). The Western diet, a dietary pattern that is generally characterized by high intakes of saturated fats, sugars, and refined carbohydrates, activates the innate immune system and impairs adaptive immunity, leading to chronic inflammation and impaired host defense against viruses. In fact, consumption of unhealthy diets could pose an amplified risk to severe COVID-19 pathology. In this specific contest, wider access to healthy foods should be a priority in order to reduce susceptibility and long-term complications from COVID-19.

As a conclusion, ALA has demonstrated positive effects in different pathophysiological situations in the context of the (i) inflammatory status, through the downregulation of the secretion and expression of various cytokines also involved in the "cytokine storm" that occurs also during infection by SARS-Cov-2 (mainly of IL-6, TNF-α, and IL-1β) and of various chemokines (IL-8, CCL2, and RANTES); (ii) oxidative stress, by lowering ROS levels in various prooxidant situations; (iii) situations of dysregulation of the immune response, mainly by reducing the secretion of cytokines by from macrophages and increasing the polarization of macrophages toward an M2 anti-inflammatory phenotype compared to an M1 one, reducing the infiltration of neutrophils in different tissues and the presence of NPA as well as the number of monocytes.

All these situations, as widely described in this review, can also be found in patients with moderate/severe syndrome of COVID-19. A critical review analysis of these studies allows to speculate about the prophylactic effect of ALA against SARS-CoV-2 infection always taking into account the daily doses recommended by national health institutes (~1.5–3 g for adults) (National Institute of Health Office of Dietary Supplements, 2021).

Considering the near future, there is a need for clinical studies involving a greater number of patients. In addition, to study an effective preventive effect (in state of hypothetical one) that these compounds could have in reducing the risk and severity of the COVID-19, it is necessary to take a longer period of time.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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