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Ascorbic Acid: Its Role in Immune System and Chronic Inflammation Diseases

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Abstract: Ascorbic acid (AA), also known as vitamin C, was initially identified as the factor preventing the scurvy disease, and became very popular for its antioxidant properties. It is an important co-substrate of a large class of enzymes, and regulates gene expression by interacting with important transcription factors. AA is important in all stressful conditions that are linked to inflammatory processes and involve immunity. It has been known for decades that the persistence of an inflammatory stimulus is responsible for the onset of many diseases. AA is essential to stimulate the immune system by increasing the strength and protection of the organism. Therefore, its immunostimulant, antinflammatory, antiviral and antibacterial roles are well known, we have summarized its main functions in different types of diseases related to the immune system and chronic inflammation. We can conclude that AA, due to its effects and diversity of regulated pathways, is suitable for use in various fields of medicine including immunology, toxicology, radiobiology and others. AA is not preferable to be used as an isolated mode of treatment, but it can be co-applied as an adjuvant to regulate immunity, gene expression and other important physiological processes. However, we propose that future studies will take into consideration the research of new combinations of antioxidant natural substances and drugs.

Keywords: Antinflammatory role, antiviral role, ascorbic acid, chronic diseases, immune system, inflammation.

INTRODUCTION

Ascorbic acid (AA), also known as vitamin C, is a small carbohydrate molecule first identified in the 1920s by Albert von Szent Györgyi, who discovered its role in the scurvy prevention and cure. This disease is a pathological life-threatening condition suffered by people who do not have access to fruit or vegetables for long periods of time [1]. Natural sources of AA are citrus fruits, green leafy vegetables, strawberries, papaya, broccoli, etc [2]. Apart from humans, it is also vitally important to other species such as animals and plants. The surprising point that is some animals (some fish, birds, and a few mammals, including guinea pigs and humans) have lost the capability to produce it over the course of evolution while some species of plants and animals, such as cats and dogs, are able to biosynthesize it from glucose in the liver [1]. AA is an essential dietary nutrient for the biosynthesis of collagen and is a co-factor in the biosynthesis of catecholamines, L-carnitine, cholesterol, amino acids, and some peptide hormones. For these functions it is implicated in different diseases [3].

AA is a gluconic acid lactone derived from glucuronic acid and a water-soluble ketolactone with two ionizable hydroxyl groups [4]. It is one of the naturally occurring antioxidants present in equal parts as D-ascorbic acid (AA) and L-ascorbic acid (LAA) being its chemically active form. These molecules are essentially isomeric and are mutually interchangeable [2]. AA is reversibly oxidized, forming the stable ascorbic free radical (AFR) intermediate with the loss of one electron or dehydroascorbic acid (DHA) with the loss of two electrons. AFR decays by disproportionation to AA and DHA, whereas DHA spontaneously hydrolyzes under physiological conditions, with the opening of the lactone ring to form diketogulonic acid (DKG) [5].

Due to its strong reducing potential, AA is involved in numerous metabolic processes. In particular, it plays a role in hydroxylation reactions catalyzed by some mono and dioxygenases like prolyl 4-, prolyl 3- and lysyl hydroxylase, trimethyl lysine and γ-butyrobetaine hydroxylase, dopamine β-hydroxylase, 4-hydroxyphenylpyruvate dioxygenase and HIF prolyl 4-hydroxylase. These oxygenases catalyze the cotranslational hydroxylation of proline and lysine residues in the procollagen, the tryptophan hydroxylation in serotonin biosynthesis, the catecholamines synthesis, the α-amidation in the biosynthesis of numerous peptide hormones such as gastrin, cholecystokinin, calcitonin, vasopressin and oxytocin, β-hydroxy-γ-N-trimethyllysine and γ-butyrobetaine hydroxylation in endogenous carnitine synthesis [6-10]. Moreover, it has a role in iron transfer both in transporting protein transferrin and in storing protein ferritin and is involved in the detoxification of numerous substances in the

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liver by stimulating the cytochrome P450 synthesis, and in the promotion of intestinal iron absorption by reducing nearly non-absorbable Fe^{3+} to more easily absorbable Fe^{2+} and by inhibiting the production of insoluble iron-tannin and iron-phytate complexes [4].

The ascorbate and dehydroascorbate transport is mediated by different systems [11]. More specifically, AA is transported by sodium-dependent transporters such as SVCT1 and SVCT2 [11, 12] whereas several tissues utilize the transport of DHA by the GLUTs, integral membrane proteins [13].

AA has antioxidant or prooxidant characteristics depending on the redox potential of the surrounding environment [14]. For these reasons, in recent years it has been widely studied as an adjunct in the treatment of various diseases including cancer. It seems indeed that its cytotoxic activity relies on its ability to generate reactive oxygen species (ROS) rather than on its popular antioxidant action. Although paradoxical, AA may have prooxidant and even mutagenic effects in the presence of transition metals. However, the mechanism underlying the production of this latter species is unclear [16]. Physiologically, AA is a potent free radical scavenger in the plasma, protecting cells against oxidative damage caused by ROS. Its antioxidant property is attributed to its ability to reduce potentially damaging ROS, forming, instead, resonance-stabilized and relatively stable ascorbate free radicals [16]. This mechanism is manifest in a number of cytoprotective functions under physiological conditions, including prevention of DNA mutation induced by oxidation, protection of lipids against peroxidative damage, and repair of oxidized amino acid residues to maintain protein integrity [17]. Whether AA functions as an antioxidant or prooxidant is determined by at least three factors: i) the cellular environment redox potential, ii) the presence/absence of transition metals and iii) the ascorbate local concentrations. This last factor is particularly relevant in treatments that depend on the antioxidant/prooxidant property of AA, because it can be readily manipulated and controlled "*in vivo*" to achieve desired effects [18].

AA and Immune System

The immune system requires appropriate energy and nutrient supplies which are important for the immune system because its individual components are characterized by high turnover rates, leading to a higher substrate requirement compared to most other body systems [4]. In an immunobiological context, AA has been the most studied micronutrient being essential to ensure the efficient working of the immune system (see Table **1**). Immunocompetent cells such as lymphocytes, neutrophils, and monocytes have AA concentration 10- to 100-fold higher than the plasma concentration and accumulate it against a concentration gradient [19]. There are also evidences of biokinetic association between AA dose and immune cell concentration that underlines its specific function in the cellular immune response [20]. A lack of AA in the diet is the primary cause of scurvy. This can occur in people on highly restricted diets, who are under extreme physiological stress such as during an infection or after an injury, and in chronic alcoholics. Early signs of the disease are bleeding gums and bleeding under the skin, causing tiny pinpoint bruises. The deficiency can progress to the point that it causes poor wound healing, anemia, and impaired bone growth. The body normally stores about 1,500 mg of AA at a time, and symptoms of a deficiency do not occur until the body pool is less than 300 mg. It would take several weeks on a diet containing no AA for this drop to occur in an otherwise well-nourished person. [21]

A study has shown that in healthy men the reduction of AA intake for 60 days, from 250 to 5, 10, or 20 mg per day, leads to a lower immune response as shown by a delayed-type skin reaction which is considered as an appropriate marker for immune response. Even after increasing AA intake to 60 mg/d or 250 mg/d for three weeks, the immune responses in these subjects were still lower than prior to the start of the study [22]. AA has been shown to stimulate the immune system by enhancing T-lymphocytes proliferation in response to infection leading to an increased cytokine production and immunoglobulin synthesis. [23].

On the other hand, high doses of supplemental AA may attenuate exercise-induced inflammatory reactions, even if anti-inflammatory effects were not observed in healthy men supplemented with AA for a long period [24]. Furthermore, AA resulted to affect also antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis and delayed-type hypersensitivity [25]. Many studies in humans and other species underlined the AA functional significance in infection resistance [20]. During the course of infections, there is a rapid depletion of cellular AA that returns to normal after recovery. DHA has shown much stronger antiviral activity for AA due to several factors such as free

Table 1. Ascorbic acid in immune system.

Ascorbic acid and immune system	References
Physiological concentrations increase lymphocytes proliferation; supraphysiological concentrations inhibit proliferation.	[24-26]
Enhance cytokines production and synthesis of immunoglobulins in response to infection.	[27]
High doses may attenuate exercise-induced inflammatory reactions.	[28]
Affects antimicrobial and natural killer cell activities, lymphocytes proliferation, chemotaxis and delayed-type hypersensitivity.	[29]
Viruses multiplication inhibition.	[30]
Up-regulation NK cells activity.	[35]

radicals rather than an antioxidant mechanism [26]. In addition, Furuya *et al*. have demonstrated that AA weakly inhibited the multiplication of different families of viruses such as herpes simplex virus type 1 (HSV-1), influenza virus type A and poliovirus type 1 [26]. The antiviral effect of DHA might be caused by its binding to the virus or molecules involved in viral replication. The mode of characterization of DHA antiviral activity against HSV-1 has revealed that its addition 11 hours after infection can inhibit the formation of progeny virus in the infected cells, suggesting that it affects the HSV-1 multiplication after the completion of viral DNA replication, probably at the stage of maturation, i.e., the assembly of progeny virus particles, although involvement of other step(s) in the multiplication process cannot be excluded [26].

AA deficiency reduces resistance to various microbial agents, such as bacteria including *Mycobacterium tuberculosis* and Rickettsia, as well as fungal infections such as *Candida albicans* [20]. Stephensen CB *et al*. demonstrated that plasma ascorbate levels were lower in subjects with HIV infection, which suggests that such subjects have greater AA requirements than those without HIV infection [27].

Moreover, it has been demonstrated that inflammation induced by *Helicobacter pylori* infection in the stomach causes significantly enhanced AA consumption and reduces its secretion into the gastric lumen suggesting its protective role against *Helicobacter pylori* associated gastric carcinogenesis by enhancing mucosal immune responses [28-30]. AA is one of the well-known antiviral agents, especially to influenza virus. Some studies have investigated whether AA could regulate influenza virus infection *in vivo* by using Gulo (-/-) mice, which cannot synthesize AA like humans, after intranasal inoculation of influenza virus H3N2/ Hongkong [31]. Since AA up-regulates NK cell activity through the regulation of activating/inhibiting receptors on the NK cells surface, it is commonly known that AA and NK cells are closely related to the prevention of common cold and the flu [32]. However, when Gulo (-/-) mice were supplemented with AA after virus inoculation, a viral replication definite suppression was not observed. Hence there are evidences of the importance of AA concentration at the initial stage of influenza virus infection, so damages through the replication of influenza viruses can be effectively prevented when AA concentration is sufficiently high at the initial stage of viral infection. However, if it is insufficient, the influenza virus pathogenesis could not be prevented. Therefore, AA plays a critical role in *in vivo* anti-viral immune responses against influenza virus through the increase of IFN-IL-1α/β production. Hence, maintaining sufficient plasma AA levels, by the continuous uptake through the diet or supplement, could effectively prevent *in vivo* pathogenesis of influenza virus at the initial stage of viral infection [31].

AA and Chronic Inflammation

The main function of the mammalian immune system is to monitor tissue homeostasis, to protect against invading or infectious pathogens and to eliminate damaged cells [33]. Inflammation is a physiological process crucial for the function of the innate immune system as it is a response to acute tissue damage, whether resulting from physical injury, ischemic injury, infection, exposure to toxins, or other types of trauma. Inflammation may become chronic either because an inflammatory stimulus persists or because of dysregulation in the control mechanisms that normally turns the process off [34].

The general activity of AA as an antioxidant implies that conditions associated with chronic inflammation and oxidative stress would lead to its depletion. Numerous inflammatory conditions including gastritis, bowel diseases and gastro-intestinal disorders, type 2 diabetes and obesity, lung inflammations, neurodegenerative diseases, and cardiovascular disease are all associated with marked reduction in plasma of AA levels as compared to healthy controls (see Table **2**) [35].

Inflammatory Bowel Diseases

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease and ulcerative colitis that present in both acute and chronic inflammation even if their etiologies are unknown [36, 37]. Nutritional deficiencies are common in IBD patients and antioxidants appear to play a special role in protection of the intestinal cells from inflammation. Several studies point to critical depletion of AA, selenium, zinc, and vitamin E in IBD patients. AA and zinc must be supplemented carefully, particularly because of their potential to cause gastrointestinal upset. Serum and leucocyte AA levels are low in adult and pediatric patients with Crohn's disease, both in the case of active and remission disease [38]. Colonic biopsies of inflamed vs. non-inflamed areas in patients with Crohn's disease showed a 35% reduction in total AA content whereas in patients with ulcerative colitis, the total AA content was reduced by 73% [39]. Also, in these patients different biomarkers of lipid peroxidation are higher [38] and decreased during AA and vitamin E supplementation [40]. The decreased antioxidant defenses may severely compromise the inflamed mucosa, rendering it more susceptible to oxidative tissue damage, hindering recovery of the mucosa and return of epithelial cell layer integrity. The loss of chemical antioxidant components provides a strong rational for developing novel antioxidant therapies for the IBD treatment. Recent studies suggest that MitoQ may have potential as a novel therapeutic agent for the treatment of acute phases of inflammatory bowel disease [41].

Coeliac disease (CD*)* is a common gastro-intestinal disorder caused by a hypersensitivity reaction to wheat gliadin and similar proteins from rye and barley, affecting genetically predisposed individuals (HLA-DQ2/DQ8). The current treatment is a life-long strict gluten-free diet (GFD) [42, 43]. Bernardo D *et al*. showed that the addition of AA to culture medium of duodenal explant decreases the secretion of inflammatory mediators in response to gluten in CD patients. Supplementation of a non-toxic AA concentration (20 mM) to gliadin challenged biopsy culture not only inhibited the gliadin-induced production of nitrites, but also downregulated the secretion of pro-inflammatory cytokines such as IFN-α, TNF α, IFN-γ, and IL-6. This decrease could be the result of the inhibition of the NF-kB pathway induced

Table 2. Ascorbic acid in inflammatory diseases.

Inflammatory diseases	Ascorbic Acid role	References
Inflammatory bowel diseases	• In Crohn's disease and in ulcerative colitis protects the mucosa by inflammation, rendering it less susceptible to oxidative tissue damage.	[44, 45]
	• In Coeliac disease reduces mucosal inflammatory response to gluten and secretion of pro-inflammatory cytokines. It inhibites NF-kB pathway.	[48]
Lung inflammations	• It acts on lung function with protective effects against infection.	[50-54]
	• Positive role in chronic rhinosinusitis.	[55-57]
	• Role in cystic fibrosis transmembrane conductance regulator chloride channel.	[58]
Heart diseases	• It protects against oxidative stress.	[59]
	• Role in inflammatory and oxidative prevention and modulation associated with atrial fibrillation and atherosclerosis.	[63-66]
Neurodegenerative diseases	• In Alzheimer's disease it protects against oxidative stress and inflammation; it prevents apoptosis and cell death in neuroblastoma cells.	[68, 69]
	• In Parkinson's disease it has neuroprotective effects against oxidative-induced neuronal death.	[71]
	• No association between AA intake and Amyotrophic Lateral Sclerosis progression.	[72]
	• To be explored the role of AA in Multiple Sclerosis.	[73, 74]
Obesity and type 2 diabetes	• Role on modulation adipocyte lipolysis, glucocorticoid release from adrenal glands.	[86-88]
	• Role on hyperglycemia improvement and glycosylation in obese diabetic mice.	
Chronic obstructive pulmonary disease (COPD)	• Improvement DNA resistance in whole blood WBC against oxidative challenge.	
	• Benefic effect on skeletal muscle fatigue.	[52, 53]

by AA. Moreover, AA is resulted to affect IL-15 pathway since this interleukin is considered to be a central cytokine in CD immunopathogenesis for its capacity to initiate the innate immune response to gliadin and to activate dendritic cells. Finally, AA is capable also of inhibiting dendritic cells activation, blocking cytokine secretion and the immunostimulatory properties [44].

Lung Inflammations

Evidence of AA oxidation has been seen in adult respiratory distress syndrome [45]. Adults with mild asthma exhibit decreased AA in lung fluid and increased glutathione oxidized (GSSG) concentrations which, in the presence of normal plasma concentrations, are suggestive of oxidative stress in the airways [46]. Cross-sectional studies showed an inverse relation between plasma AA and lung inflammation and suggested that high plasma AA concentrations or exogenous intakes had a positive impact on lung function [47, 48]. Low maternal AA intake during pregnancy was associated with asthma in 5-year-old children that showed reduced AA concentrations in leucocytes (50 %) and plasma (35 %) [49]. Some clinical studies showed that AA supplements of 2 g/d exerted protective effects on airway responsiveness to viral infections and allergens, but had little effect on exercise-induced asthma although one study reported attenuated exercise-induced bronchoconstriction in patients with asthma [46, 50].

Chronic obstructive pulmonary disease (COPD) in which the lungs lose their inherent springiness, making it progressively harder to breathe, can have a dramatic effect on the ability to exercise and even perform simple activities of daily life because of the disease's fallout effects on skeletal muscles. Several factors have been implicated in these muscle problems. These include loss of fitness from inactivity, problems with the part of cells that convert fuel to energy caused by the COPD itself, and oxidative stress. Some research suggests that easing oxidative stress could improve skeletal muscle function. According to various studies it appears that the administration of multiple antioxidants could be a more effective mode used in the treatment of COPD [51] In particular, vitamin E or C supplementation for 12 weeks may improve the resistance of DNA in whole blood WBC against oxidative challenge in patients with COPD, although more research is needed to demonstrate the beneficial effect on slowing the decline of lung function in patients with COPD [52]. Therefore, Rossman MJ *et al*. demonstrated a beneficial role of AA administration on skeletal muscle fatigue in patients with COPD and further implicated systemic oxidative stress as a causative factor in the skeletal muscle dysfunction [53].

Chronic rhinosinusitis (CRS) refers to inflammation of the contiguous tissues of the upper respiratory tract, where insult to the nasal mucosa also affects adjacent sinus tissue and involves the physiological disruption of the mucus membranes by particulates, allergens, infection, and immune system dysregulation [54]. A prospective trial examined blood levels of various vitamins and minerals in children with CRS compared to healthy age-matched controls. AA,

vitamin E, copper, and zinc levels resulted significantly lower in the chronic sinusitis group compared to controls [55]. In a clinical trial, intranasal AA was used to treat allergic rhinitis; in details, 48 subjects received either AA solution (n=27) or placebo (n=21) sprayed into the nose three times daily. After two weeks, 74% of subjects treated with the AA solution exhibited a decrease in nasal secretions, blockage and edema, compared to controls [56].

Cystic fibrosis (CF) is an inherited disease characterized by the buildup of thick, sticky mucus that can damage many of the body's organs mostly lungs. It is caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR) that is required to regulate the components of sweat, digestive fluids, and mucus. It regulates the movement of chloride and sodium ions across epithelial membranes, such as the alveolar epithelia located in the lungs. AA is present in the respiratory lining fluid of human lungs, and local deficits occur in oxidative stress conditions. AA controls the cystic fibrosis transmembrane conductance regulator chloride channel because it is a biological regulator of CFTR-mediated Cl secretion in epithelia. AA, in the respiratory tract, represents a potential nutraceutical and pharmaceutical target for the complementary treatment of sticky airway secretions by enhancing epithelial fluid secretion [57].

Heart Diseases

Heart disease (also called cardiovascular disease) is a class of diseases that involve the heart, the blood vessels or both. As with the other antioxidants, AA helps to prevent heart disease by preventing free radicals from damaging artery walls, which could lead to plaque formation. Low levels of AA have been associated with a number of conditions, including high blood pressure, gallbladder disease, stroke, some cancers, and atherosclerosis, the build-up plaque in blood vessels that can lead to heart attack and stroke. This nutrient also keeps cholesterol in the bloodstream from oxidizing, another early step in the progression towards heart disease and stroke. It is thought that is protects against oxidative stress by reducing the levels of free oxygen radicals and inhibiting low density lipoprotein oxidation and oxidative cell damage [58]. AA may help people who have marginal AA status to obtain favorable blood cholesterol levels. Getting enough AA from diet by eating lots of fruits and vegetables may help reduce the risk of developing some of these conditions. However, there is no conclusive evidence that taking AA supplements will help or prevent any of these conditions [59].

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, affecting approximately 0.9% of the population [60, 61]. AA is a potent oxygen scavenger, which may potentially modulate the inflammatory and oxidative abnormalities associated with AF [62]. In 2001, Carnes *et al*. gave supplemental AA to 43 patients before, and for 5 days following cardiac bypass graft surgery, and found that AA significantly reduced the incidence of post-operative AF. AA resulted in attenuating atrial electrophysiological remodeling and in reducing AF burden, possibly via scavenging peroxynitrite and other reactive oxygen species and reducing the inflammatory substrate [63]. In another study AA is reported to reduce the early recurrence of AF following successful cardioversion. Actually, when compared to baseline values, inflammatory indices were decreased after cardioversion in patients receiving AA, but did not change significantly in the control group [64].

Atherosclerosis is a disease of initial inflammation and subsequent oxidative damage and AA has the potential to counteract both of these processes. While a role for AA in preventing human atherosclerosis still remains to be defined, mounting evidence supports a role for the AA in preventing endothelial dysfunction, plaque stabilization, and macrophage-dependent oxidative modification of LDL [65].

Neurodegenerative Diseases

Neurodegenerative disease is an umbrella term for a range of conditions which primarily affect the neurons in the human brain. These are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. This causes ataxias, or dementias. The common neurodegenerative diseases are predominantly idiopathic disorders of unknown pathogenesis.

In Alzheimer's Disease (AD), the oxidative stress is suggested to play a major role in its pathogenesis [66]. Several studies provided evidence to support a therapeutic role of AA in AD [67, 68]. Orally administered AA reduced oxidative stress and proinflammatory cytokines induced by Aβ peptide injections in the CA1 area of the hippocampus in rat brains [67]. In a study testing whether AA might protect cultured SH-SY5Y neuroblastoma cells from apoptotic cell death, AA pretreatment prevented apoptosis as well as cell death due to β-amyloid protein [68]. Additionally, AA pretreated cells also showed a decrease in basal rates of endogenous β-amyloid generation. Furthermore, AA has been reported to decrease acetylcholinesterase activity in mice, an action analogous to that of the more common antidementic drugs [69]. AA was also demonstrated to affect the release of acetylcholine from synaptic vesicles. Combining other antioxidants with AA may prove beneficial for AD prevention by providing a more comprehensive activation of pathways to reduce oxidative stress. In fact, it decreases β-amyloid generation and acetylcholinesterase activity and prevents endothelial dysfunction by regulating nitric oxide, a newly discovered factor in AD pathogenesis and progression [66].

Parkinson's disease (PD) is a degenerative disease of the brain characterized by the degeneration and progressive loss of dopaminergic neurons. It affects parts of the brain that are associated with normal movement and balance. Although the etiology of PD is not completely understood and is believed to be multifactorial, oxidative stress and mitochondrial dysfunction are widely considered major consequences, which provide important clues to the disease mechanisms. Reports have revealed that PD neurodegeneration is linked to dietary habits in which a deficiency of antioxidant compounds such as folic acid, vitamins (A, C, E, and niacin), and selenium in the body increases the risk for PD. Several evidences have shown that brains of PD patients have low levels of endogenous antioxidants, increased dopamine

oxidation, and high iron levels, suggesting that oxidative stress is a key element in the pathophysiology of PD and a significant target to counteract the progression of the disease. Ascorbic acid has been proposed as a therapeutic agent for preventing and delaying the development of PD. It has shown neuroprotective effects against oxidative-induced neuronal death. The neuroprotective role of vitamin in neurodegenerative diseases has been linked to its potent antioxidant activity [70].

Amyotrophic lateral sclerosis (ALS), often referred to as "Lou Gehrig's Disease," is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. The progressive degeneration of the motor neurons in ALS eventually leads to their death. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. With voluntary muscle action progressively affected, patients in the later stages of the disease may become totally paralyzed.

AA could also favorably affect ALS risk. Animal studies of familial ALS have indicated that although AA supplementation prior to disease failed to delay age at onset, it significantly slowed down the progression of paralysis. However, several small case–control studies did not observe an association between AA intake and ALS progression. Neither supplemental use nor high dietary intake of AA appeared to affect the risk of ALS. AA long-term supplementation was also not associated with ALS risk [71].

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. Similarly to other neurodegenerations, MS is characterized by a series of biochemical changes affecting neuronal functions to different extent; great attention has been given to oxidative/ nitrosative stress and to alterations in mitochondrial functions. The serum metabolic profile has been evaluated in a group of MS patients which resulted in AA decrease, demonstrating that MS induced alteration in energy metabolism and in oxidants/antioxidants balance [72]. Yet the role of antioxidant vitamin supplementation in the prevention and/or treatment of MS remains to be explored [73].

Some people use AA for depression, thinking problems, dementia, physical and mental stress, fatigue, and attention deficit-hyperactivity disorder (ADHD). It is well known that oxidative stress plays a role in the pathogenesis of stress-induced depression. Several studies in mice model have demonstrated an association between stressful conditions and the onset of clinical depression highlighting the ascorbic acid antioxidant role in the treatment of this disease [74]. Therefore, a randomized, double-blind, placebo-controlled pilot study about antidepressants used to treat pediatric patients suggests that AA may be an effective adjuvant agent in the treatment of major depressive disorder (MDD) in pediatric patients [75].

Obesity and Type 2 Diabetes

Obesity is emerging as one of the major health threats [76]. Indeed, it is well known that an excessive body fat accumulation, which defines this disease, could lead to several associated clinical manifestations such as type 2 diabetes, metabolic syndrome features, cardiovascular events, and arthritis [77]. These effects are related to a white adipose tissue (WAT) overgrowth and also to an impaired production and secretion of endogenous products by the enlarged adipocytes or the macrophages coexisting in the tissue [77], which often have pro-inflammatory properties [78]. Actually, it has been reported that several inflammatory molecules, such as TNF-α, IL-6, MCP-1 and iNOS (inducible NO synthase), correlate with increased body adiposity and inflammatory-related pathways are activated in obesity and insulin resistance states [79-81]. Indeed, leptin, which is related to the control of food intake and energy expenditure, and adiponectin, which is related to significant insulin sensitivity improvements, are metabolically relevant in this disease [82-84]. On the other hand, in obesity, a mitochondrial dysfunction and ROS overproduction as well as an association between oxidative stress and insulin resistance have been observed [85]. Furthermore, depletion of the antioxidant defenses has also been described in obesity [86]. Beneficial effects of AA on obesity-related mechanism have been described: the modulation of adipocyte lipolysis [87-89], glucocorticoid release from adrenal glands, hyperglycemia improvement and glycosylation decrease in obese diabetic mice [90], and an inhibition of the inflammatory response [91]. In a study [92] the effects of AA incubation on epididymal rat adipocyte metabolism and secretory functions have been described *in vitro*. The glucose uptake inhibition observed in adipocytes without insulin treatment, and under insulin treatment, could be partially explained by the fact that DHA possibly competes with glucose for GLUT1 and GLUT3, and for GLUT4 transporters respectively [93]. However, it was reported previously that in primary cultures of rat hippocampal neurons, AA accumulation inhibited the glucose transport inside the cytoplasm independently of this competition [94]. Regarding the secretion and expression of some adipokines, a study [92] has demonstrated an important AA inhibitory effect on leptin secretion, which is in agreement with the previously reported reducing effects on leptin circulatory levels of a diet with AA supplementation given to high-fat diet-fed rats for 56 days [95]. However, the results of that study suggested that leptin secretion inhibition was mainly due to specific effects of the AA treatment over the adipocytes and not due to mass-reducing effects on the leptin secretor tissue [92].

CONCLUSION

The data summarized in this review indicate that AA, due to its effects and diversity of regulated pathways, is suitable for use in various fields of medicine including immunology, toxicology, radiobiology and others. The supplementation of AA improves the immune system functions, such as antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis and delayed-type hypersensitivity. Although AA is not a miracle drug and can even induce some adverse effects, its potential in medicinal chemistry is quite high. In particular consensus from literature is that consumption of AA supplemental leads to no significant adverse health effects to humans in general. Individuals who have a history of kidney stone formation and those who experience iron overload should exercise caution before using AA supplemental, especially in the doses exceeding daily recommended dietary allowance which may result in

oxalate crystallization and formation of advanced glycation. Occasionally, individuals experience diarrhea or mild nausea [96].

Additional AA uses include counteracting the side effects of cortisone and related drugs, and aiding drug withdrawal in addiction. A drug-lipid interaction studies suggest that ascorbic acid prevented lipid peroxidation induced by Sterodin, is a novel non-specific immunostimulating drug produced by a combination of bile lipids and bacterial metabolites [97].

Moreover aspirin, in combination with ascorbic acid, was reported to have a possible synergistic effect in neuronal cells, which might have important implications for the treatment of neuroinflammatory conditions [98]. In addition, aspirin plus ascorbic acid presented an antioxidative effect, and by this effect, proinflammatory cytokine production should be reduced [99]. Thus, anti-inflammatory therapy might be successful with lower doses of aspirin when combined with ascorbic acid, thereby avoiding the side effects of the usually required high dose aspirin treatment, and adding the antioxidant benefits of ascorbic acid [98].

Despite all the information available on AA, we still do not know what the optimal treatment level should be for humans. Significant advantages of AA include low cost, minimal or no toxicity and simple application. AA is not preferred to be used as an isolated mode of treatment, but it can be co-applied as an adjuvant to regulate immunity, gene expression and other important physiological processes. Therefore through researches, evaluations, and collaborations, future studies should be better targeted to the identification of new combinations of antioxidant natural substances and drugs.

CONFLICT OF INTEREST

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

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