Received: 29 December 2021 | Revised: 9 March 2022 | Accepted: 17 March 2022

DOI: 10.1002/rmv.2348

WILEY

REVIEW

Antioxidant/anti-inflammatory effect of Mg^{2+} in coronavirus disease 2019 (COVID-19)

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Funding information

Programa de Apoyo a la Investigación y el Posgrado (PAIP), Grant/Award Number: 5000-9105; Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica (PAPIIT), Grant/Award Numbers: IN202219, IN200922; Consejo Nacional de Ciencia y Tecnología (CONACYT) México, Grant/Award Number: A1-S-7495

Abstract

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), characterised by high levels of inflammation and oxidative stress (OS). Oxidative stress induces oxidative damage to lipids, proteins, and DNA, causing tissue damage. Both inflammation and OS contribute to multi-organ failure in severe cases. Magnesium (Mg^{2+}) regulates many processes, including antioxidant and anti-inflammatory responses, as well as the proper functioning of other micronutrients such as vitamin D. In addition, Mg^{2+} participates as a second signalling messenger in the activation of T cells. Therefore, Mg^{2+} deficiency can cause immunodeficiency, exaggerated acute inflammatory response, decreased antioxidant response, and OS. Supplementation with Mg^{2+} has an anti-inflammatory response by reducing the levels of nuclear factor kappa B (NF-κB), interleukin (IL) -6, and tumor necrosis factor alpha. Furthermore, Mg^{2+} supplementation improves mitochondrial function and increases the antioxidant glutathione (GSH) content, reducing OS. Therefore, Mg^{2+} supplementation is a potential way to reduce inflammation and OS, strengthening the immune system to manage COVID-19. This narrative review will address Mg^{2+} deficiency associated with a worse disease prognosis, Mg^{2+} supplementation as a potent antioxidant and anti-inflammatory therapy during and after COVID-19 disease, and suggest that randomised controlled trials are indicated.

KEYWORDS

COVID-19, inflammation, magnesium deficiency, oxidative stress, post-COVID-19 manifestations, SARS-CoV-2

Abbreviations: 4-HNE, 4-hydroxynonenal; ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin II; ATP, adenosine triphosphate; CAT, catalase; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; E protein, envelope protein; eNOS, endothelial nitric oxide synthase; ETC, electron transport chain; GCL, γ-glutamyl-cysteine ligase; GCSF, granulocyte-colony stimulating factor; GGT, γ-glutamyl-transpeptidase; GPx, glutathione peroxidase; GR, glutathione reductase; GS, glutathione synthetase; GSH, glutathione; GST, glutathione S-transferase; H_2O_2, hydrogen peroxide; ICU, intensive care unit; IFN-γ, interferon-gamma; IL, interleukin; IP-10, interferon-γ-inducible protein 10; M protein, membrane protein; MagT1, magnesium transporter 1; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; Mg^{2+}, magnesium; $MgSO_4$, magnesium sulphate; MIP-1A, macrophage inflammatory proteins; N protein, nucleocapsid protein; NF-κB, nuclear factor kappa B; NK, natural killer; NKG2D, NK activator receptor; non-ICU, non-intensive care unit; NOXs, NADPH oxidases; Nrf2, nuclear factor erythroid 2-related factor 2; nsps, non-structural proteins; O_2, oxygen; $O_2^{\cdot-}$, superoxide radical; OH, hydroxyl radical; ORF, open reading frame; OS, oxidative stress; PAF, platelet-activating factor; pp, polyprotein; RBD, receptor-binding domain; ROS, reactive oxygen species; RTC, replication and transcription complex; S protein, spike glycoprotein; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; SOD, superoxide dismutase; TCR, T cell receptor; TF, tissue factor; TMPRSS2, transmembrane protease serine 2; TNF-α, tumour necrosis factor-alpha; VDBP, vitamin D binding protein; VDR, vitamin D receptor; XMEN, X-linked immunodeficiency with Mg^{2+} deficiency, Epstein-Barr virus infection, and neoplasia; XO, xanthine oxidase.

1 | INTRODUCTION

SARS-CoV-2 produces coronavirus disease 2019 (COVID-19), which has caused more than 4.6 million deaths worldwide.[1] COVID-19 is associated with inflammation and oxidative stress (OS) conditions, inducing respiratory and cardiac complications, such as respiratory insufficiency and arrhythmias. In addition, COVID-19 patients also may submit minor complications like dry cough, fever, fatigue, sore throat, and diarrhoea.[2-4]

Scientific publications have been shown that nutritional status and nutrition habits are relevant in developing different comorbidities associated with higher mortality in COVID-19.[5-7] In this sense, magnesium (Mg^{2+}) deficiency causes low-grade chronic inflammation and OS.[8-10] It has led to the hypothesis that Mg^{2+} supplementation might improve the severity of COVID-19 disease,[11,12] including a possible intervention of Mg^{2+} in SARS-CoV-2 infection by inhibiting the activity of proteases required for protein S cleavage.[12] Therefore, this narrative review focuses on the effect of Mg^{2+} to prevent developing severe COVID-19 from the perspective of Mg^{2+} deficiency, which could contribute to an antioxidant/anti-inflammatory development in COVID-19 and post-COVID-19 manifestations. We also proposed that Mg^{2+} supplementation like a potential therapy might ameliorate COVID-19 effects and post-COVID-19 sequels. Our exhaustive review of the scientific literature was conducted in the 'PubMed databases'. Search keyword terms included all possible combinations, abbreviations, and synonyms between 'magnesium', 'immune system', 'magnesium deficiency', 'magnesium supplementation', 'oxidative stress', 'inflammation', 'COVID-19', 'SARS-CoV-2', 'thrombosis', 'post-COVID-19 manifestations'. We also considered the publication date from March 1971 to October 2021.

2 | SARS-CoV-2 VIRAL LIFE CYCLE

The SARS-CoV-2 virus has been identified as a single-stranded RNA-enveloped (positive sense), spherical or pleomorphic beta coronavirus of the *Coronaviridae* family. SARS-CoV-2 infects lung and intestinal epithelial cells via the angiotensin-converting enzyme 2 (ACE2) receptor, causing mild to moderate upper respiratory and gastrointestinal infections (Figure 1).[2,13,14] SARS-CoV-2 can also bind to the central nervous system cells by alternative receptor CD147, expressed in high levels in the brain, producing neurological symptoms such as headaches, vision changes, dizziness, ataxia, or impaired consciousness.[15]

SARS-CoV-2 virion has an outer surface with 24 to 40 spike glycoproteins (S protein; divided into S1 and S2), which fuse with different human cells such as nasal cavity cells.[16] The latter bidding is performed by the receptor-binding domain (RBD) in the protein S1 subunit, which binds specifically at ACE2 (Figure 1).[17] ACE2 is the predominant host cell receptor, and this is the critical protein for SARS-CoV-2 to invade susceptible cells.[14,18,19] Moreover, SARS-CoV-2 employs the transmembrane protease serine 2 (TMPRSS2) and the proprotein convertase furin (host cell proteases) to primes the S protein, triggering viral envelope fusion with the host cell membrane.[20,21] Then, the virus enters basal cells by activating different endocytosis pathways, such as clathrin-dependent endocytosis, or directly releasing the SARS-CoV-2 genome into the cytosol.[22] Both routes allow the viral genome to reach the cytosol, where the SARS-CoV-2 RNA genome unwraps from its viral envelope to translate the viral polyproteins (pp).[17,22]

In the cytosol, the SARS-CoV-2 RNA genome is translated in two large open reading frames (ORF), ORF1a and ORF1b, inducing the expression of the individual non-structural proteins (nsps) and polyprotein 1a (pp1a) and 1b (pp1ab).[17,23] The nsps comprise the viral replication and transcription complex (RTC) that includes RNA-processing. The nsps also reorganise the host membranes, where the SARS-CoV-2 RNA will replicate and structural viral proteins will be expressed.[23] Once the viral genome has been amplified, nucleocapsid proteins (N protein) encapsulate it, where membrane proteins (M protein) and envelope proteins (E protein) ensure SARS-CoV-2 incorporation in the viral particle during the assembly process (Figure 1). Finally, virions are secreted from the infected cell by exocytosis to attach to another cell surface.[17,24]

3 | INFLAMMATION, OXIDATIVE STRESS, AND COVID-19

During SARS-CoV-2 viral life cycle, SARS-CoV-2 is exposed to the innate defence system, developing pronounced inflammation and, in acute cases, severe acute respiratory syndrome (SARS) or multi-organ failure, called in general terms, COVID-19.[25,26] During COVID-19 and its pronounced inflammation increase the secretion of interleukin (IL) -1β, IL-4, IL-10, interferon-gamma (IFN-γ), interferon-γ-inducible protein 10 (IP-10), and monocyte chemoattractant protein 1 (MCP-1).[27,28] Furthermore, COVID-19 produces several nuclear factor kappa B (NF-κB)-mediated cytokines, including IL-6 and IL-8 (Figure 2).[29] COVID-19 also induces elevated plasma levels of pro-inflammatory cytokines (tumour necrosis factor-alpha (TNF-α), IL-2, IL-6, and IL-1β).[28,30] In addition, COVID-19 patients from the intensive care unit (ICU) show elevated levels of IL-7, IL-10, MCP1, granulocyte-colony stimulating factor (GCSF), IP-10, and macrophage inflammatory proteins (MIP-1A).[27] The latter promotes hyper-inflammation, hyperpyrexia, and organ failure.[31] Organ failure results in respiratory failure, acute cardiac complications, respiratory distress syndrome, organ dysfunction, septic shock, and in critical cases, causes death. Therefore, organ failure spreads mortality risk.[32]

T cell response in developing protective immunity is essential in regulating inflammation. For example, an adequate T cell response reduces the overactivation of the inflammatory response (Figure 2). On the other hand, the suppression or deficient T cell activity increases the burden on macrophages and monocytes, exacerbating the inflammatory process, distinctive of COVID-19 (Figure 2).[33-35] Laboratory results showed decreased T helper lymphocytes ($CD3^+$, $CD4^+$) and suppressor T lymphocytes ($CD3^+$, $CD8^+$). These cells control infections and prevent overactivity of the immune system

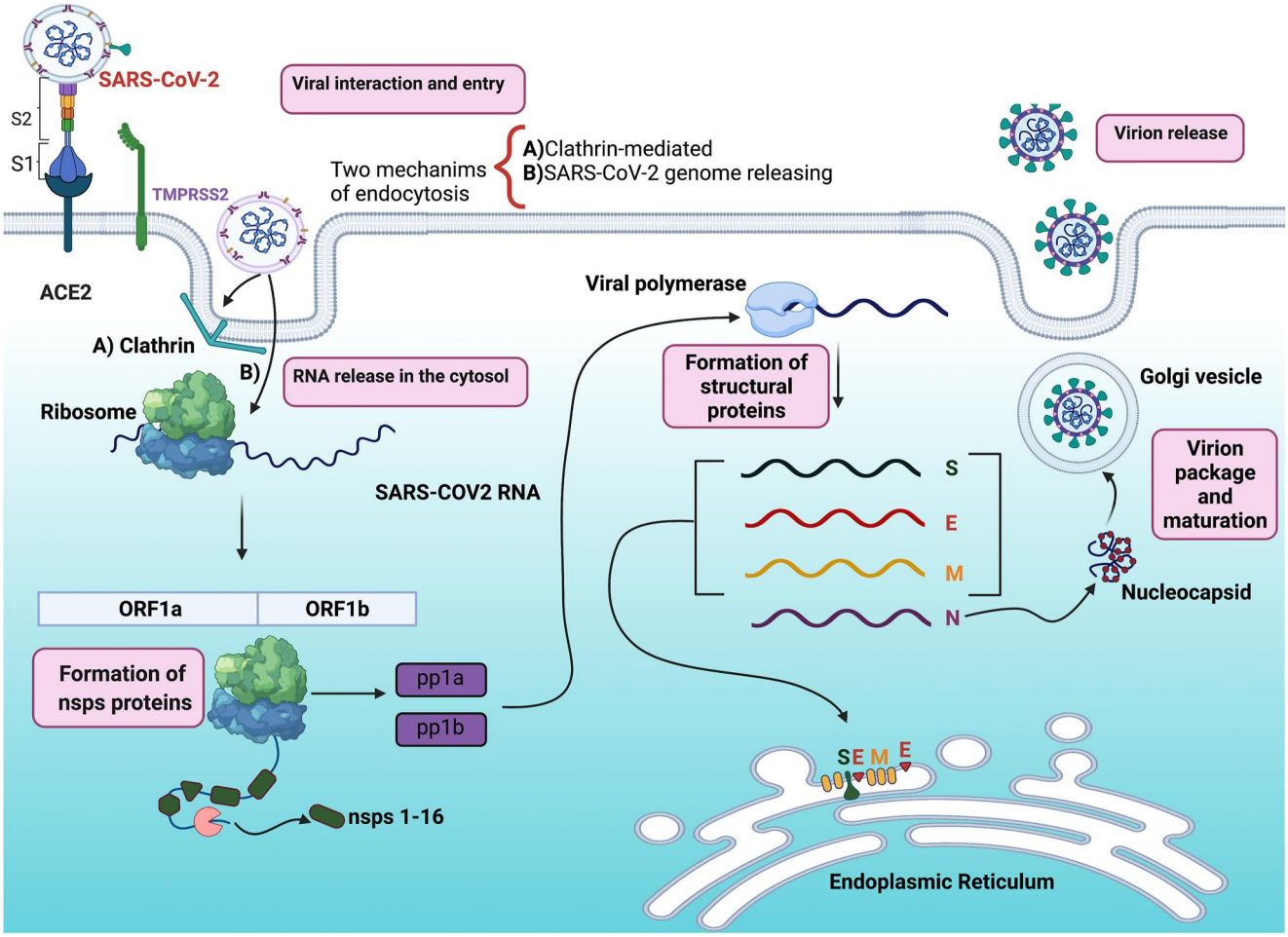

FIGURE 1 The viral life cycle of severe acute respiratory syndrome coronavirus type 2 (SARS-COV-2). SAR-COV-2 interacts with angiotensin-converting enzyme 2 (ACE2) receptor and then the transmembrane protease serine 2 (TMPRSS2) and proprotein convertase furin primes S protein for entry into target cells. Two endocytosis mechanisms are known that SARS-CoV-2 uses for entrance to the cell: (a) clathrin-mediated and (b) the releasing direct of its genome into the cytosol. Both mechanisms permit the viral genome to reach the cytosol, and once released, SARS-CoV-2 is translated into two open reading frames (ORF): ORF1a and ORF1b, promoting the expression of non-structural proteins (nsps) 1–16, and the polyprotein 1a (pp1a) and pp1b. The latter allows the replication of the viral structural proteins: spike (S), envelope (e), the membrane (M), and the nucleocapsid (N). S, E, and M form the viral capsid, and N organises the nucleocapsid. Finally, the virion is packaged and released outer the infected cell. The figure was created with BioRender

and uncontrolled virus infection.[30] Following the latter, Zhang et al.[26] reported an impaired immune response related to deficit T cell function in patients infected with SARS-CoV-2. Since there is an impaired T cell function, the inflammatory process exacerbates inflammation with an uncontrolled increase in levels of pro-inflammatory cytokines and chemokines (cytokine storm), producing multi-organ failure due to tissue damage. Therefore, the cytokine storm is associated with COVID-19 severity.[35]

Inflammation also produces reactive oxygen species (ROS), and if these ROS are not attenuated, OS is triggered, inducing oxidative damage to proteins, lipids, and DNA. Regarding lipids, its oxidation results in lipids radicals, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE),[36] which are highly reactive, causing DNA damage (Figure 2). The latter induces cell cycle arrest to permit DNA repair and proteostasis; however, if oxidative damage persists, apoptosis cell death is promoted.[37] A study in deceased COVID-19 patients showed elevated 4-HNE levels in the lungs, associated with lethal outcomes, suggesting that deceased COVID-19 patients have a critical failure of the antioxidant response.[38] Furthermore, the MDA levels are increased in ICU and non-intensive care unit (non-ICU) patients, compared with healthy groups.[39,40] Therefore, these works suggest a close relationship between antioxidant response and COVID-19 severity.

ROS overproduction during SARS-CoV-2 infection has been attributed to NADPH oxidases (NOXs) activation, principally NOX2. It has been shown that NOX2 is upregulated during COVID-19 infection.[41] Supporting the latter, SARS-CoV-2 S protein together IL-6 activate NOX2, producing high ROS levels in endothelial cells (Figure 2).[42] Moreover, NOX2 is stimulated by angiotensin II (Ang II), which plasma levels are elevated in COVID-19.[43] Indeed, the upregulation of Ang II has been associated with the overstimulation of NOXs and the consequent production of ROS.[44,45]

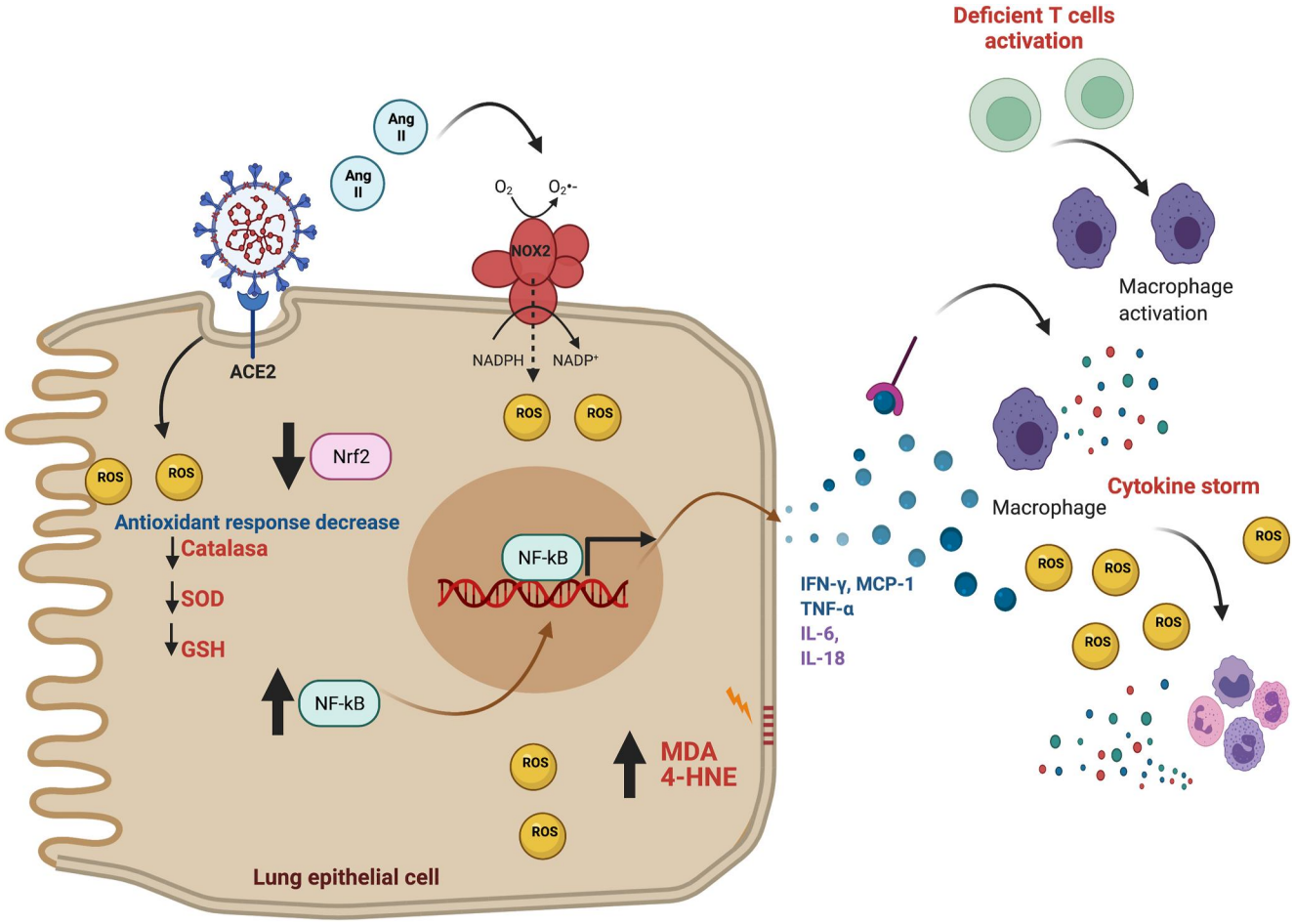

FIGURE 2 Inflammation and reactive oxygen species (ROS) overproduction during coronavirus disease 2019 (COVID-19) infection. The interaction between angiotensin convertase enzyme 2 (ACE2) receptor and severe acute respiratory syndrome coronavirus type 2 (SARS-COV-2) generates ROS through angiotensin II (Ang II) because the latter stimulates NADPH oxidase 2 (NOX2). Moreover, the antioxidant response decreases through SARS-CoV-2 infection by lessening catalase, superoxide dismutase (SOD), and glutathione (GSH). ROS overproduction oxidises lipids in the cell membranes, generating the products of lipid peroxidation malondialdehyde (MDA) and 4-hydroxinonenal (4-HNE), which are increased In COVID-19 deceased patients. On the other hand, SARS-CoV-2 activates the nuclear factor kappa B (NF-κB), inducing the secretion of several cytokines and chemokines that include interferon-gamma (IFN-γ), tumoral necrosis factor-alpha (TNF-α), interleukin (IL) 6 (IL-6), IL-18, and monocyte chemoattractant protein 1 (MCP-1). The latter and the deficient inactivation of T cells prompt macrophages activation, inducing the production of other cytokines, triggering cytokine storm accompanied by ROS overproduction. The figure was created with BioRender

Although some antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD) increase at the onset of COVID-19 disease, suppressing the overproduction of ROS and OS,[39] in progressive stages of COVID-19, these enzymes significantly decrease along with plasma levels of vitamins (A, C, E), glutathione (GSH), as well as cofactors of antioxidant enzymes like manganese and copper.[40] These data suggest that COVID-19 patients are prone to a deficient antioxidant system during the progression of COVID-19.

In conclusion, although the antioxidant and anti-inflammatory responses are present at the beginning of SARS-CoV-2 infection, both are downregulated during COVID-19 development, resulting in OS and inflammation. Therefore, the uncontrolled inflammatory and insufficient antioxidant response related to OS may be the principal mechanism in multi-organ failure during COVID-19.

4 | MAGNESIUM, INFLAMMATION AND OXIDATIVE STRESS

Around 600 enzymes require Mg^{2+} as a cofactor, while other 200 enzymes need Mg^{2+} as an activator to realise their functions (Figure 3).[46] Thus, Mg^{2+} is crucial for energetic metabolism, protein, and amino acid synthesis, and maintenance of the electrical potential in tissues and cell membranes.[47,48] Mg^{2+} also participates in bone mineralisation, muscle relaxation, and neurotransmission (Figure 3).[49] In addition, Mg^{2+} regulates lipid composition, stabilising the cellular membrane and reducing its fluidity and permeability.[50,51] Furthermore, Mg^{2+} is also involved in most reactions in which adenosine triphosphate (ATP) functions as a cofactor. For example, ATP-Mg^{2+} complexes are required for the activity of glycolytic enzymes such as

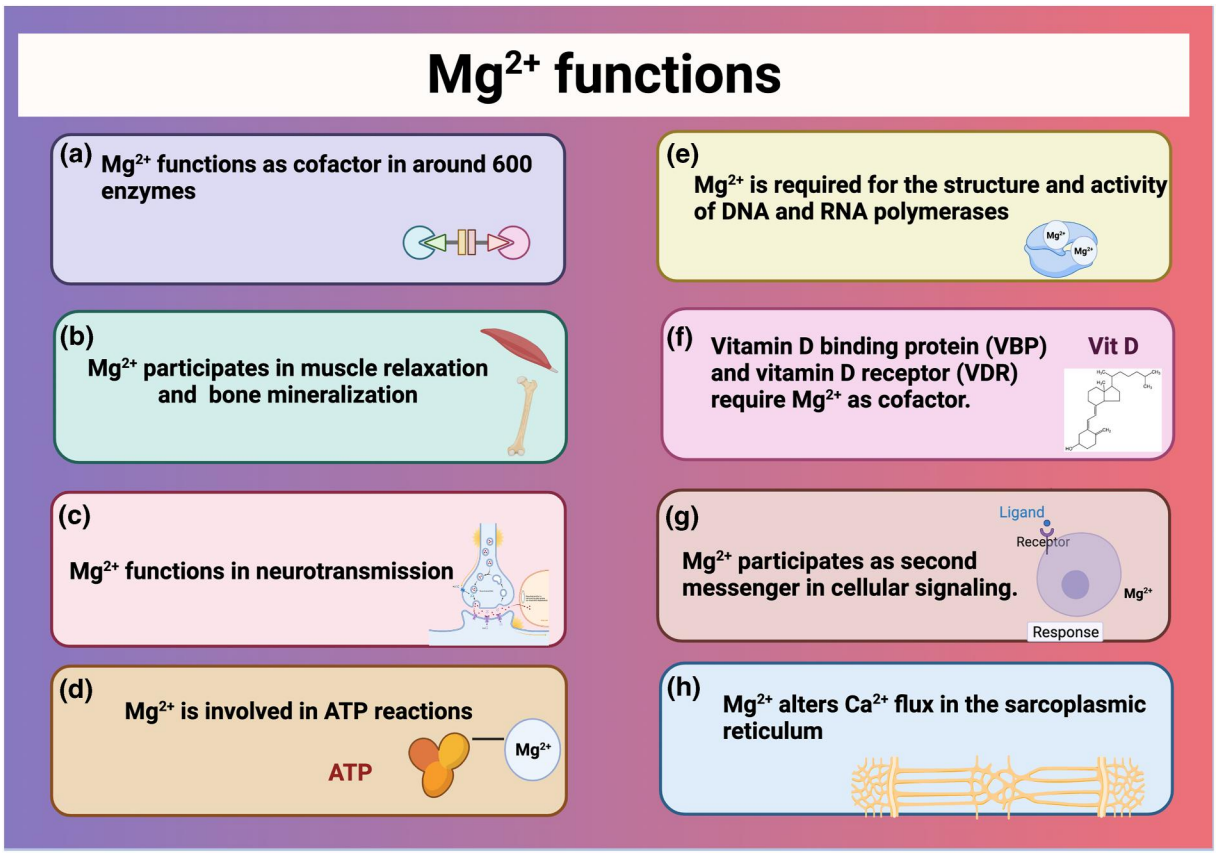

FIGURE 3 Functions of magnesium (Mg^{2+}). In the figure, the roles of Mg^{2+} have been listed (A-H)

hexokinase, phosphofructokinase, aldolase, phosphoglycerate kinase, and pyruvate kinase (Figure 3).[52]

Mg^{2+} is required for the structure and activity of DNA and RNA polymerases since it contains 2 Mg^{2+} binding sites, essential for conformational changes of the enzymes during catalytic reactions.[53] Vitamin D and vitamin D, enzymes responsible for vitamin D metabolism, require Mg^{2+} as a cofactor to bind to vitamin D (Figure 3). Mg^{2+} is also necessary for 25-hydroxylation of vitamin D in the liver and 1α-hydroxylation in the kidneys.[54] Mg^{2+} participates in different cell signal pathways, functioning as a second messenger.[55,56] Finally, Mg^{2+} alters Ca^{2+} flux in the sarcoplasmic reticulum, which modifies the permeability of the protons in the mitochondrial membrane, altering oxidative phosphorylation (Figure 3).[57]

4.1 | Magnesium and immune system

As described above, Mg^{2+} is involved in essential enzymatic reactions in the cells, including immune response. Mg^{2+} has a closer relationship in adaptative immunity, related to cellular signalling and immunomodulatory pathways.[52,56,58] Mg^{2+} has been described as a second signalling messenger in T cells, promoting their activation.[56,59] In individuals with X-linked immunodeficiency with Mg^{2+} deficiency, Epstein-Barr virus infection, and neoplasia (XMEN), the magnesium transporter 1 (MagT1) is downregulated in immune T cells.[56] Since MagT1 is essential for T cell receptor (TCR) stimulation and T cell activation, its downregulation is related to immunosuppression in XMEN patients.[60]

The reduction of free intracellular Mg^{2+} causes defective expression of the natural killer (NK) activator receptor (NKG2D) on $CD8^+$ T and NK cells, decreasing their cytolytic responses (Figure 4).[60] NK and $CD8^+$ T cells' functions are essential for controlling viral infections because these cells induce apoptotic cell-infected death, a regulated programed cell death that does not induce inflammation, and defects in this type of cell death might cause excessive viral load.[61] Since these cells are decreased, the innate immune cells such as macrophages and neutrophils are activated to control the infection, promoting exacerbated immune response by triggering cytokine storm (Figure 4).[60,61] In this understanding, strengthening NKs and T cells activation through Mg^{2+} supplementation could be associated with a better prognosis of COVID-19. In contrast, Mg^{2+} deficiency may promote inflammation due to the deficient activation of cytolytic response in $CD8^+$ T cells and NK cells.[56,59,60]

Different preclinic studies have also demonstrated that Mg^{2+} deficiency leads to exaggerated acute inflammatory response, such as increased circulating pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), leucocytosis, increased plasma levels of complement component C3, and the marked elevation of circulating substance P, especially after

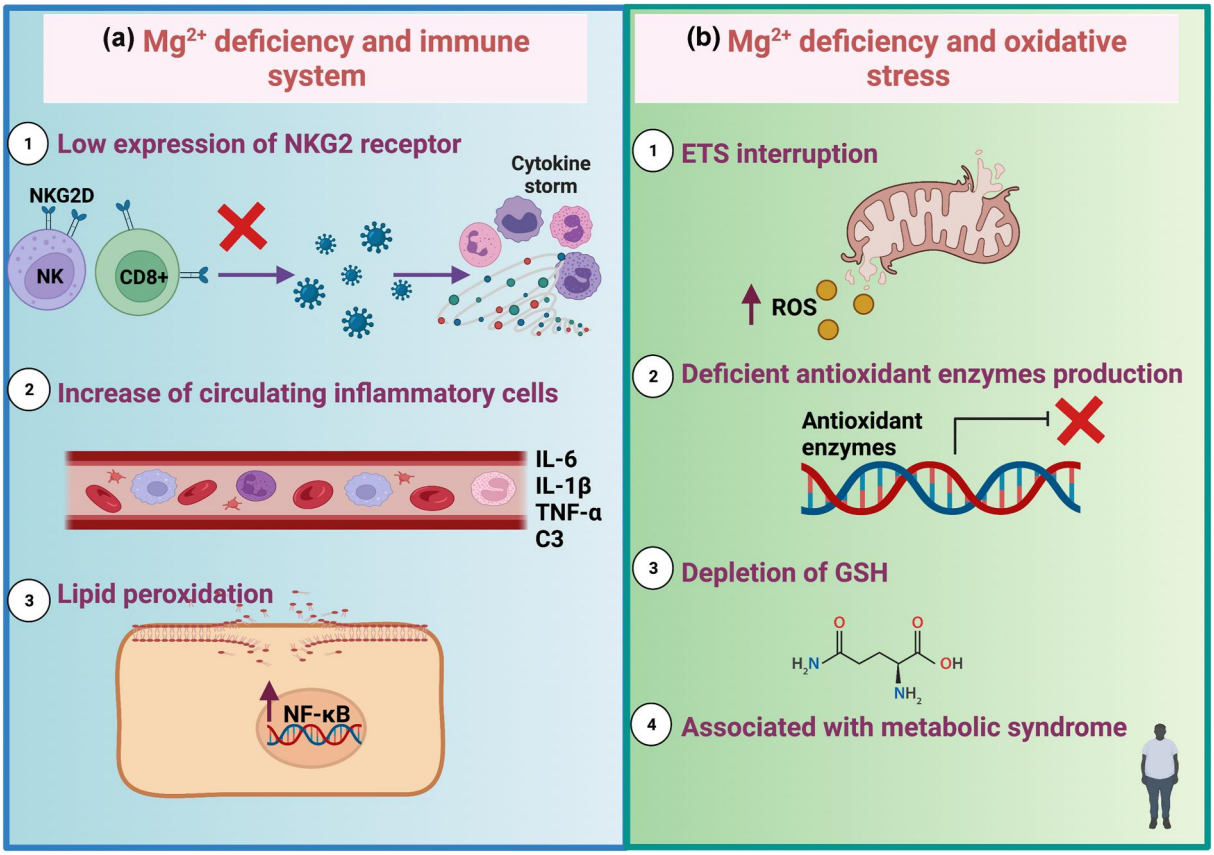

FIGURE 4 Magnesium (Mg^{2+}), immune system, and oxidative stress (OS). (a) Mg^{2+} deficiency related to the immune system produces the (1) low expression of the natural killer (NK) activator receptor (NKG2D) on the T $CD8^{+}$ cells, promoting a mild or no anti-inflammatory response to viruses. Consequently, a cytokine storm is triggered. (2) Moreover, circulating inflammatory cells augment, inducing the production of interleukin (IL) 6 (IL-6), IL-1β, tumoral factor-alpha (TNF-α), and complement system C3. (3) Mg^{2+} deficiency induces lipid peroxidation, which activates nuclear factor kappa B (NF-κB). Mg^{2+} also induces oxidative stress by promoting (1) electron transfer system (ETS) interruption, generating reactive oxygen species (ROS) production. Furthermore, (2) the production of antioxidant enzymes is deficient, and (3) glutathione (GSH) is depleted because of anormal Mg^{2+} levels. (4) Mg^{2+} deficiency is also associated with metabolic syndrome and low-grade chronic inflammation, such as obesity, diabetes, and cardiovascular diseases

immune stress (Figure 4).[9,62-66] Mg^{2+} deficiency induces the *Novo* synthesis of ceramide and lipid peroxidation, activating NF-κB.[67,68] NF-κB is involved in the transcription of inflammatory genes such as cytokines (IL-1β and TNF-α).[61,69-71] The latter means that Mg^{2+} deficiency can be related to inflammation by itself.

Imbalance Mg^{2+} levels are a decisive factor in mortality in COVID-19 cases. A retrospective study by Alamdari et al.[3] found that older patients of Teheran Iran with hypomagnesaemia have a higher risk of mortality due to COVID-19. Moreover, Quilliot et al.[72] found an association between Mg^{2+} and COVID-19. This group conducted a cohort study, demonstrating low serum Mg^{2+} concentrations in hospitalised COVID-19 adult patients. The serum concentrations of Mg^{2+} revealed that 73.7% of the patients had hypomagnesaemia, showing that most of the patients are located in serious to severe cases.[72] These studies reveal that hypomagnesaemia is more frequent in patients with COVID-19, possibly associated with the severity of the disease. In this way, the severity of the COVID-19 disease might be strongly related to the pro-inflammatory state in Mg^{2+} deficiency patients.

Sugimoto et al.[73] reported that Mg^{2+} therapy during inflammatory states decreases NF-κB, IL-6, and TNF-α. A similar beneficial effect is observed in the inflammatory marker C reactive protein (CRP), which levels are decreased.[74] Moreover, optimal Mg^{2+} status enhances vitamin D functionality that regulates inflammation by promoting an anti-inflammatory effect.[75,76] Although the molecular mechanism of the relationship between Mg^{2+} and inflammation is poorly described, even more in COVID-19, it is clear that during Mg^{2+} supplementation decreases inflammation markers.

Mg^{2+} could also indirectly be involved in the immune response by modulating the gut microbiome. For instance, it has been reported that diets containing Mg^{2+} can change microbiome composition.[77-83] In contrast, Mg^{2+} deficiency can lead to dysbiosis.[77,79] Dysbiosis refers to quantitative or qualitative changes in the composition of the normal microbiota that causes a microbial imbalance, playing an essential role in susceptibility to infectious diseases.[84] Many studies have associated altered gut microbiome with the severity of COVID-19, producing dysbiosis[84-89] while restoring Mg^{2+} levels could benefit the diversity and health of the gut microbiome. Moreover, the use of

probiotics and prebiotics for preventing and treating COVID-19 could modulate the gut microbiome.[84,88,89] Therefore, Mg^{2+} usage could be able to mitigate systemic inflammation by regulating microbiome, preventing dysbiosis.[77,90-92]

4.2 | Magnesium and oxidative stress

Aerobic living systems use oxygen (O_2) for many processes. For instance, in mitochondria, to produce energy in the form of ATP, O_2 is the final electron acceptor in the electron transport chain (ETC).[93] However, electron leakage reduces O_2 to superoxide radical ($O_2^{\cdot-}$). It is the most reactive radical during this process. $O_2^{\cdot-}$ also be produced in cytosol by different enzymes such as NOXs or xanthine oxidase (XO) or in the endoplasmic reticulum by cytochrome p450 reductase or cytochrome b5.[36] The antioxidant system can reduce $O_2^{\cdot-}$ into hydrogen peroxide (H_2O_2) by different enzymes such as SOD or NOX4.[36] H_2O_2, in turn, is reduced to H_2O by CAT, glutathione peroxidase (GPx), or glutathione reductase (GR), among others. $O_2^{\cdot-}$ and H_2O_2 can react together or with some metals in Fenton and Haber-Weiss reaction inducing hydroxyl radical ($^{\bullet}OH$), a highly reactive ROS that generates different biomolecules damage.[36] Thus, these ROS have been maintained at low concentrations in a redox balance. Low ROS concentrations are associated with cellular signalling; however, if redox balance cannot be maintained, ROS levels increase induces OS and oxidative damage.[36,93] Therefore, the establishment of cellular antioxidant responses must be fast and efficient to neutralise the potential oxidant effects of ROS.

Low consumption and the consequent deficient status of Mg^{2+} have been associated with antioxidant response decrease, and, in consequence, OS increase (Figure 4).[8,58,94,95] Moreover, in a state of intracellular Mg^{2+} deficiency, a reverse flow of Mg^{2+} in the mitochondria is induced, promoting the ETS interruption and mitochondrial decoupling, which increases ROS production.[96] Adding to this increase of ROS, the low availability of Mg^{2+} decreases the production of antioxidant enzymes, leading to OS.[97,98] Mg^{2+} participates as an indirect antioxidant due to being a cofactor of enzymes that produce GSH, mitigating the effects of OS in the stabilisation of the cell membrane (Figure 4).[99,100] Also, during OS and proinflammatory states, the treatment with organic Mg^{2+} salt such as magnesium isoglycyrrhizinate and magnesium lithospermate B induces activation of nuclear factor erythroid 2-related factor 2 (Nrf2).[101-103] This transcriptional factor modulates gene transcriptions and protein expressions of antioxidant enzymes such as CAT, SOD, and GPx.[101,104] Evidence shows that Mg^{2+} deficiency is associated with increased OS and cytokine due to antioxidant defences decrease in different cardiovascular diseases such as hypertension.[10,94,105,106] Furthermore, moderate or subclinical Mg^{2+} deficiency prepares phagocytic cells to release pro-inflammatory cytokines that lead to chronic oxidative and inflammatory stress.[107] Therefore, Mg^{2+} deficient status reduces antioxidant defence and increases inflammation, producing OS.

Regarding GSH, a nonprotein tripeptide conformed by glycine, cysteine, and glutamate, is an essential and the highest ubiquitous intracellular antioxidant.[108,109] Therefore, it has multiple important biological functions, including maintaining the normal cellular oxidation-reduction state, cell signalling, and antioxidant functions due to reducing particular ROS such as H_2O_2.[110] Also, GSH can maximise the activity of the other antioxidants such as vitamin C through glutathione S-transferase (GST). GST catalyses the glutathione-dependent reduction of dehydroascorbate, restoring their antioxidant function.[111,112] It has been shown that GSH depletion frequently occurs due to insufficient Mg^{2+} concentrations in acute deficiency.[94,105,106] That is, some enzymes that catalyse the biosynthesis reaction of GSH and maintain its correct operation require Mg^{2+}. For example, γ-glutamyl-cysteine ligase (GCL) and glutathione synthetase (GS) are enzymes completely dependent on ATP, requiring Mg^{2+} as a cofactor.[105,113,114] Also, γ-glutamyl-transpeptidase (GGT) uses Mg^{2+} as an activator of this enzyme.[115-117] A study published by Mohammadi et al.[118] reported that magnesium sulphate ($MgSO_4$) significantly decreased oxidative damage caused by hypoxia in mouse brains. In addition, Mg^{2+} supplementation improves mitochondrial function and increases the content of GSH in mitochondria.[118,119] Also, $MgSO_4$ was effective as a treatment for preeclampsia, significantly promoting GSH production and thus suppressing ROS production.[120] As described in this section, Mg^{2+} deficiency represents a risk factor for maintaining an optimal oxidation-reduction state, leading to OS development. Thus, chronic Mg^{2+} deficiency has severe oxidative implications such as lipid peroxidation, causing general cellular dysfunction and even cell apoptosis associated with inflammation and OS.[94,121]

Mg^{2+} deficiency is frequently associated with is a strong relationship between OS and metabolic syndrome, associated with low-grade chronic inflammation, such as obesity, diabetes, and cardiovascular diseases (Figure 4).[8,58] For instance, the increase in lipid peroxidation and OS was observed in a study of obese women with Mg^{2+} deficient diets, which presented low Mg^{2+} concentration in erythrocytes.[122]

Because Mg^{2+} has multiple functions in the body, its deficiency has been related to chronic inflammatory and OS, which can compromise the immune response, inducing individuals more prone to infection such as SARS-CoV2. Thus, nutritional supplementation may strengthen the immune system to manage COVID-19.

5 | MAGNESIUM CONSUMPTION DURING COVID-19 AND POST-COVID-19 DISEASE

In addition to inflammatory and OS conditions, low Mg^{2+} consumption is associated with a higher incidence of diabetes and cardiovascular diseases.[96,123-126] Both diseases are associated with a worse prognosis in COVID-19, according to the meta-analysis published by Gold et al.[127] Furthermore, COVID-19 patients with serum concentrations of Mg^{2+} ≤0.75 mM (low concentrations) are the most frequent hospital admissions.[3,72] Considering the above, we suggest that the frequent consumption of foods high in Mg^{2+} might prevent severe COVID-19 symptoms. The diet can provide the primary

source of Mg^{2+}.[128] For instance, whole-grain cereals (Mg^{2+} in pericarp) are considered the best dietary source of Mg^{2+}; even part of the observed benefit with whole-grain cereals intake is due to Mg^{2+}.[129,130] Also, leafy-greens foods such as chard, spinach, purslane (due to chlorophyll), and nuts are good sources of Mg^{2+}. Some other foods consumed more frequently also have high levels of Mg^{2+}, such as dark chocolate, black beans, soy nuts, and some other seeds (Table 1).[131,132]

Kopf et al.[134] reported that the correct daily intake of fruit, vegetables, and whole grains significantly decreased levels in some inflammatory markers such as the lipopolysaccharide-binding protein, TNF-α, and, IL-6. Therefore, the latter suggestion points out that increasing Mg^{2+} intake through food has favourable effects. Moreover, the severity of COVID-19 cases are related to respiratory insufficiency or acute respiratory distress syndrome (indicator: low O_2 saturation); coagulopathies (indicator: elevated D-dimer, prothrombin time prolongation); inflammation (indicator: elevated CRP (an indicator of active acute inflammation), IL-6); multi-organ damage: liver damage (indicator: hypoalbuminemia), and lymphopenia.[3,72,135] Thus, these symptoms can be reduced by Mg^{2+} supplementation. For instance, it has been observed that concomitant supplementation of vitamin D, vitamin B12, and Mg^{2+} in COVID-19 patients can decrease ICU admission incidence and O_2 therapy requirements.[11]

5.1 | Respiratory insufficiency and magnesium supplementation

Inflammation markers in COVID-19 severity could be directly related to serum Mg^{2+} levels. Chronic obstructive pulmonary disease (COPD) and COVID-19 show high levels of systemic inflammatory markers, such as CRP, leucocytes, IL-6, IL-8, and fibrinogen. Both diseases also present the same mechanisms in endothelial dysfunction, including vascular inflammation and OS. Furthermore, both COPD and COVID-19 reduce mediators that promote vasodilation such as endothelial nitric oxide synthase (eNOS).[28,30,38,136-141] It has been demonstrated that COPD severity was associated with serum Mg^{2+} deficiency and a worse quality of life in COPD patients.[142] In line with this, Mukerji et al.[143] demonstrated that intravenous adjuvant therapy with $MgSO_4$ improves bronchodilator therapy in acute exacerbations of COPD. Additionally, intravenous $MgSO_4$ as adjuvant therapy benefits moderate to severe acute asthma, a disease with high levels of inflammation and OS, by acting as a bronchodilator and improving pulmonary functions.[144-146] Since COPD, asthma and COVID-19 present systemic inflammation, it is suggested that Mg^{2+} supplementation might enhance lung function in cases of respiratory failure in COVID-19. Together these shreds of evidence suggest that complementary therapy with Mg^{2+} reduces the symptoms of inflammatory respiratory diseases and improves respiratory functions. Therefore, Mg^{2+} may be a potential therapy in cases of COVID-19 respiratory failure due to exacerbated inflammation, preventing their development at severe.

Another aspect that may be related to respiratory failure is diaphragm dysfunction, implying a partial or complete diaphragm function loss.[147,148] McCool and Tzelepis[149] mentioned that 'Diaphragmatic dysfunction is an underdiagnosed cause of dyspnoea.' In this sense, a possible cause of respiratory failure in COVID-19 may be diaphragm dysfunction; however, this area has been poorly explored. Interestingly, it has been reported that prolonged mechanical ventilation causes diaphragm dysfunction.[150] However, van Steveninck and Imming[151] reported a case of diaphragm dysfunction before intubation and mechanical ventilation in a COVID-19 patient. This suggests that diaphragm dysfunction without mechanical ventilation or intubations may also be related to others processes, such as sepsis due to SARS-CoV-2. Sepsis is a massive inflammatory response characterised by OS, cytokines, and mitochondrial dysfunction.[152,153] In a prospective study, Demoule et al.[154] reported that sepsis contributes to the development of diaphragmatic dysfunction in ICU admissions. It has been shown that elevated TNF-α and IL-6 in diaphragm dysfunction is strongly associated with OS, driving muscle contractile dysfunction and atrophy.[155-157] Whidden et al.[155] demonstrated the use of Trolox (a potent antioxidant) attenuated diaphragmatic contractile dysfunction and prevented skeletal muscle loss, concluding that preventing OS could be an optimal strategy to avert diaphragm weakness. On the other hand, Jiang et al.[158] reported that $MgSO_4$ protects against diaphragm dysfunction caused by sepsis, attenuating the loss of diaphragm force by reducing inflammation through TLR4/NF-κB pathway inhibition. In this understanding, if diaphragm dysfunction caused by sepsis contributes to respiratory failure in COVID-19, Mg^{2+} therapy could attenuate OS and inflammation, avoiding respiratory insufficiency.

5.2 | Coagulopathies, inflammation, and OS: magnesium supplementation

During COVID-19 infection, fibrinogen and circulating D-dimer levels are elevated, inducing hypercoagulation.[159] Coagulation is a consequence of innate and adaptative immunity activation. It has been shown that inflammation-induced coagulation is featured by tissue factor (TF) activation and upregulation of coagulant pathways, promoting thrombin production.[160] Although the mechanism by which a COVID-19 induced coagulopathy development is not yet fully understood, it is supposed to have started mainly by TF activation.[61,161,162] TF is expressed in monocytes and endothelial cells in response to proinflammatory cytokines (i.e., TNF-α, IL-1, IL-8, IL-6, and MCP-1), leading to the production of fibrinogen, fibrin, and thrombin. In turn, thrombin stimulates the production of the coagulation factors V, VIII, IX, and XII, resulting in thrombus formation. Increased plasma levels of D-dimer are frequently used as an indicator of coagulation. Moreover, it has been demonstrated that high plasma levels of D-dimer are related to coagulopathies in COVID-19.[72,161,163,164] Thus, D-dimer has been proposed to evaluate the severity of lung injury in COVID-19.[161,162] Certainly, elevated D-dimer levels have been associated with NF-κB activation in

TABLE 1 Foods and their Mg^{2+} content

Food group	Food	Amount of Mg^{2+} (mg/100 g raw food)
Nut and seed	Pumpkin seeds	550
	Chia seeds	392
	Brazil nuts	376
	Sesame seeds	345
	Cashew nuts	292
	Almond nuts	270
	Peanuts	168
Legumes	Black beans (mature seeds)	171
	Soy nuts	145
	Lentils	47
	Chickpeas	45
	Green peas	33
Whole grain cereals	Oats	138
	Natural puffed wheat	133
	Post shredded wheat	132
Leafy greens	Chard	81
	Spinach	79
	Purslane	68
	Kale	33
	Turnip greens	31
	Watercress	21
	Green cabbage	12
Vegetables	Okra	57
	Nopal	52
	Artichoke	42
	Sweet corn	37
	Acorn squash	32
	Potato	23
	Broccoli	21
	Summer squash	18
	Red cabbage	16
	Asparagus	14
	Turnip	11
Fatty fish	Mackerel	60
	Tuna	35
	Pink salmon fish	27
	Halibut	23
Fruits	Avocado	29
	Banana	27
	Guava	22
	Papaya	21
	Fig	17
	Kiwi fruit	16
	Cantaloupe	13
	Berries	11
	Grapefruit	9
Others	Dark chocolate	132
	Whole milk	12
	Liquid yogurt	12
	Whole egg	12

Source: Collected data from U.S. Department of Agriculture-FoodData central.[133]

COVID-19 patients.[13,61,165,166] NF-κB is the common link between inflammatory and thrombotic processes by increasing cytokines (TNF-α, IL-6 and MCP-1), which activates the expression of TF, the main trigger of the coagulation cascade.[61,71,167] It has been shown that Mg^{2+} deficiency is associated with hypercoagulability and is partly mediated by excessive inflammation related to high levels of NF-κB.[168] Interestingly, Mg^{2+} supplementation reduces NF-κB expression and its activation,[73,101] which suggests that Mg^{2+} supplementation decreases cytokine production, deactivating the coagulopathy pathway. Moreover, in vitro studies show that Mg^{2+} inhibits clotting factors (prothrombin, thrombin, V, VII, IX) and reduces clotting blood.[169-171] Also, fibrin clots density and lysis time decreased with increasing Mg^{2+} concentrations.[170,172] Some authors also consider platelet-activating factor (PAF) as key in generating microthrombosis in COVID-19.[12,173] PAF has a central role in inflammation due to stimulating the activation of NF-κB. Furthermore, it has been shown that the reduction of extracellular Mg^{2+} results in a rapid increase in active PAF, inducing the NF-κB activation.[174,175] The above indicates a strong association between the Mg^{2+} deficiency and coagulopathies, where Mg^{2+} supplementation may be a potential therapy in coagulopathies associated with COVID-19.

5.3 | Post COVID-19 manifestations

Lasting effects of illness have been reported post-COVID-19, scientific community named as 'Long-COVID' to refer to the post-COVID conditions or sequels. In a study, Kamal et al.[176] collected post-COVID-19 symptoms and diseases from COVID-19 survivors, and the most common symptom was fatigue (72.8%). Other manifestations were mental disorders [anxiety (38%), dementia (28.6%), depression (28.6%), obsessive-compulsive disorder (4.9%)], pain

[joints pain (31.4%), continuous headache (28.9%), chest pain (28.9%)], dyspnoea (28.2%), blurred vision (17.1%), tinnitus (16.7%), and intermittent fever (11.1%).[176] Mandal et al.[177] reported in a post-COVID-19 follow-up that 71.9% of the patients present cough, breathlessness, and fatigue. Carfi et al.[178] and Cares-Marambio et al.[179] also reported that the main symptoms post-COVID-19 are fatigue, dyspnoea, chest pain, cough, psychological distress, and cognitive dysfunction.[176-179] The authors concluded that the severity of post-COVID-19 manifestations are related to the severity of COVID-19.[176,177]

According to a meta-analysis by Iqbal et al.[180] the most prevalent symptoms that persist beyond 12 weeks in post-COVID-19 syndrome were fatigue, dyspnoea and sleep disturbance. Thus, fatigue is the most frequent manifestation post-COVID-19. Halpin et al.[181] reported that the fatigue in post-COVID-19 patients was not associated with old age, since no differences of age was found on patients in the ICU. The latter indicates that fatigue is not related to age, as might be thought. Chronic fatigue syndrome, which could be related to COVID-19 fatigue, is characterised by low ATP levels and lipid peroxidation, indicating OS presence. Castro-Marrero et al.[182] demonstrated that OS is related to mitochondrial dysfunction. Also, Myhill et al.[183] observed a strong association between mitochondrial dysfunction and severity of chronic fatigue syndrome through the diagnostic tool 'ATP profile' that helped differentiate fatigue due to energy wastage or cellular respiration disfunction. The mitochondrial provides energy, and when there exists mitochondrial dysfunction apart from low ATP levels, another consequence is the increase of ROS. In a preclinic study, Liu et al.[119] demonstrated that in diabetic mice with mitochondrial dysfunction, the mitochondrial function was improved with dietary Mg^{2+} supplementation. They proposed that the mechanism that justifies the mitochondrial function improvement is the alteration of mitochondrial Ca^{2+} homoeostasis. Since fatigue is related to mitochondrial dysfunction, Mg^{2+} supplementation could be a therapy for post-COVID fatigue by improving this mitochondrial function.

Dyspnoea is the second most frequent symptom reported in post-COVID-19 patients.[176-180] Farr et al.[184] reported that patients who required mechanical ventilation during COVID-19 have a high prevalence of diaphragm dysfunction. They suggested that diaphragm dysfunction significantly contributes to dyspnoea in post-COVID-19 patients. Persistent dyspnoea could be a consequence of respiratory tissue damage caused by OS since the COVID-19 patients presented high levels of 4-HNE.[38,185] Thus, we suggest that dyspnoea could be attenuated with Mg^{2+} supplementation since Mg^{2+} antioxidant and anti-inflammation's functions.

6 | CONCLUSIONS

COVID-19 disease has been considered as an inflammatory disease in which OS occurs, leading to multi-organ failure mainly due to vascular epithelial damage. Some antioxidant and anti-inflammatory treatments are used to reduce damage, among them is Mg^{2+}. Despite the little evidence of Mg^{2+} supplementation in COVID-19 patients, the data indicate that Mg^{2+} supplementation decreases inflammation and OS in acute COVID-19 cases, avoiding the progression of the disease. In addition, the incorporation of Mg^{2+} in the diet can prevent pro-inflammatory and -OS, situations that make people susceptible to infections and states of exacerbated inflammation. Moreover, Mg^{2+} supplementation in post-COVID-19 may avoid fatigue and dyspnoea associated with inflammation and OS in post-COVID-19 patients. Randomised controlled trials to evaluate the effects of Mg^{2+} supplementation in COVID-19 patients on coagulopathies, inflammatory and oxidative markers would be an excellent way to investigate the direct impact of Mg^{2+} on the disease.

ACKNOWLEDGEMENTS

We gratefully acknowledge to the Postdoctoral Grant's Programme from the Consejo Nacional de Ciencia y Tecnología (CONACyT) for the postdoctoral fellow position to Alfredo Cruz-Gregorio. Ana Karina Aranda-Rivera. Wants to thank CONACyT for supporting the doctoral scholarship that she is receiving. This research was partially supported by the CONACyT México, Grants Numbers A1-S-7495; by the Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica (PAPIIT), Grant Numbers IN202219 and IN200922 of the Universidad Nacional Autónoma de México (UNAM), and by the Programa de Apoyo a la Investigación y el Posgrado (PAIP), Grant Number 5000-9105 of the UNAM.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Yalith Lyzet Arancibia-Hernández, José Pedraza-Chaverri, and Alfredo Cruz-Gregorio: conceptualisation; investigation; writing-original draft and writing – review and editing. Ana Karina Aranda-Rivera: figures, writing – review, and editing.

DATA AVAILABILITY STATEMENT

Data is openly available in a public repository that issues datasets with https://pubmed.ncbi.nlm.nih.gov/.

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How to cite this article: Arancibia-Hernández YL, Aranda-Rivera AK, Cruz-Gregorio A, Pedraza-Chaverri J. Antioxidant/anti-inflammatory effect of Mg^{2+} in coronavirus disease 2019 (COVID-19). *Rev Med Virol*. 2022;32(5):e2348. https://doi.org/10.1002/rmv.2348