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International Journal of Biochemistry & Physiology
ISSN: 2577-4360

Biologically Active Natural Compounds in SARS-Cov-2 Adherence Prevention

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Review Article

Volume 9 Issue 2

Received Date: September 24, 2024

Published Date: October 04, 2024

DOI: 10.23880/ijbp-16000258

Abstract

Taking into account the information on the mechanism of of SARS-CoV-2 development, during treatment, it is advisable to pay attention to inhibition of viral replication; reduction hypoxia; elimination drug poisoning and toxic, allergic consequences; add antioxidant therapy to prevent formation of reactive oxygen species (ROS) at recovery phase and hook up anti-inflammatory therapy. This goal could be achieved through the administration of antioxidants with anti-viral properties. For example, using superoxide dismutase mimics metalloporphyrins, metallocorroles, Mn biliverdins, Mn cyclic polyamines, Mn salens, metal oxides/salts and inducers of antioxidant protection. It is also possible to increase the antioxidant enzymes genes expression or the activity of the enzyme itself. Patients taking antibiotics for SARS-CoV-2 were more susceptible to exacerbations due to opportunistic infections, so alternatives to antibiotics with high efficacy and well-absorbed antioxidant properties are more appropriate. In this regard, vitamin C, N-acetylcysteine, and glycine, as well as melatonin, quercetin, astaxanthin, glutathione, fat-soluble vitamins, polyphenols, unsaturated fatty acids, and a number of other substances with high anti-inflammatory effects exhibit positive effect.

Keywords: Antioxidants; Reactive Oxygen Species (ROS); SARS-CoV-2; Cytokine Storm; Vitamins

Abbreviations

ROS: Reactive Oxygen Species; AOS: Antioxidant System.

Introduction

History has witnessed many epidemics that have affected human health and the economies of nations. The last epidemics of coronavirus infections occurred in

2002 and 2012, but they were characterized by relatively low prevalence [1]. The recent variant, namely SARS-CoV-2 strain, is characterized by the highest virulence and susceptibility. The high mortality rate, as well as the serious economic and social disadvantages, has made the study of the mechanisms of the disease and therapeutic methods the most pressing problem in medicine. However, the exact pathogenesis of this infection has not yet been identified, but the collected data suggest that the virus is a factor that causes polyorganic pathology and damages not only the lungs, but also the vascular wall, hemostasis. The virus is also a major contributor to comorbid pathology, characterized by an increase in reactive oxygen species (ROS) and disruption of the immune system. Virus-induced ROS and redox imbalance exacerbate the inflammatory response to SARS-CoV infection, ergo the mitochondria, the source of ROS, are closely monitored. The pathogenesis of coronavirus has been closely studied for nearly 20 years, although their effective prophylaxis and therapeutic methods have not yet been developed. There are a number of reasons for this, some of which include the ability of the virus to mutate intensively, high virulence of strains, features of the pathogenetic course, rapid spread. To date, the interaction of viral activity with oxidative stress, the effect of these relationships on cells and tissues are the leading factors in the development of acute stress syndrome, and the role of antioxidant deficiency in the genesis of infection has also been elucidated.

The active forms of oxygen formed during metabolism are of great importance, as they act as messengers in the cell. It is known that ROS-dependent kinases can stimulate inflammatory signals in the cell by increasing the expression and transcription of inflammatory genes. Activation of antimicrobial cells, including neutrophils and macrophages, and the formation of inflammatory cytokines are mainly dependent on ROS. Optimal levels of ROS in the body are provided by the enzymatic and non-enzymatic antioxidant system (AOS). When the antioxidant defenses are weakened, a condition called oxidative stress occurs. Numerous studies have shown that increased ROS accompanies all infectious respiratory viral infections, as well as HIV and hepatitis [2]. The activation of a number of pathological processes that cause complications for the body occurs along with the increase in ROS, and the development of coronavirus infection does not go beyond this rule. Coronaviruses (Latin Coronaviridae) are a class of about 40 zoonotic RNA-containing viruses that are widespread in the human population and among animals. There are 5 main types of coronaviruses, two of which (α- and β-viruses) infect humans. The first human coronavirus (HCoV-B814) was first detected in 1965 in a patient with an acute respiratory virus infection. At the beginning of the 21st century, coronaviruses were known as veterinary pathogens and did not pose a threat to humans. Coronavirus infections have been found to be moderate, with mild symptoms of the upper respiratory tract, but β-coronavirus epidemics in recent decades have overturned previous views. The SARS-CoV coronavirus, which caused China's severe acute respiratory syndrome in 2002-2003, and the Middle East coronavirus (MERS-CoV) in 2012, killed more than 10,000 people; Mortality in SARS-CoV was 10% and in MERS-CoV it was 37%. In late 2019, a new type of coronavirus, identified by the WHO as SARS-CoV-2 and causing a new severe acute respiratory syndrome (COVID-19), was identified.

Recent genetic research has shown that the virus originally appeared in bats, but whether the bats transmitted the virus to themselves is still being investigated. Epidemic SARS-CoV-2 bats in humans are closely related to two coronavirus types, bat-SL-CoVZC45 and bat-SL-CoVZXC21, which manifest themselves in the β-CoV / bat / Yunnan / RaTG 13/2013 sequence. The SARS-CoV-2 genome repeats the MERS-CoV genome by 50%, the SARS-CoV-1 genome - by 79%, and the BtRs-CoV genome - by 88%. Analysis of 86 complete and incomplete genomes of SARS-CoV-2 revealed numerous mutations in its encoded and unencoded areas, indicating that the new strain of coronavirus has extensive genetic material and its ability to evolve rapidly.

The virus is a circular pleomorphic pathogen with a lipid coating of 80-229 nm; on its surface are three pathogenic structural proteins. On the outside of the virus are crown-shaped glycoprotein protrusions (spike S-protein) designed to bind to the surface of the target cell. It has been found that spike proteins have the ability to hide from innate immunity by undergoing conformational changes. The spike protein of the SARS-CoV-2 virus binds to target cells through angiotensin converting enzyme-2 (ACE2), which forms active angiotensin. ACE2 is mainly expressed in cells of the gastrointestinal tract, kidneys, blood vessels, heart and lungs. The SARS virus can also bind to the CD147 cell receptor, also known as BASIGIN. As a result of the virus attaching to the cell, the spike protein is broken down into S1 and S2 subunits by proteolysis of the cell via type 2 transmembrane serine protease (transmembrane serine 2 protease, TMPRSS2). S1 then binds to the subunit ACE2, then the S1-RBD PD-ACE2 complex dissociates, the hydrophobic S2-FP peptide (fusion peptide) is released from S2, and activating endocytosis, the virus enters the target cell.

Then the virus permanent mechanism of action is activated: viral RNA is translated through the target cell's organelles, resulting in the formation of structural proteins necessary for virus development, which also form new SARS-CoV virions, and continue to damage new target cells. ACE2 and CD147 receptors sensitive to SARS-CoV-2 and TMPRSS2 are located on the surface of the upper respiratory tract and gastrointestinal epithelial cells, which are the entry routes of infection. The products of the virus interaction with the target

cell are recognized by specific NOD-receptors [3] involved in the formation of the polyprotein complex, the inflammasome [4]. RNA viruses induce the accumulation and activation of NLRP3-inflammasome in the early stages of the disease, this inflammasome plays a leading role in the formation of immunity against the virus. The virus metabolites produce ROS, which damage mitochondria and stimulate the release of DNA from mitochondria. Heat shock protein A1L (Heat Shock Protein A1L, HSPA1L) increases viral replication in the host cell; in SARS-CoV infection the rate of DNA methylation decreases because COVID reduces the activity of DNA methyl-transferases in epithelial cells of lung tissue. This leads to hyper expression of the A1L heat shock protein during SARS-CoV-2, and consequently the spread of the virus [5]. In contrast to strains with low virulence, SARS-CoV-2 has the ability to damage type I and II alveocytes, as well as endothelial cells by passing into the lower respiratory tract. This process results in the transcription expression and of anti-inflammatory cytokines. During the cytokine secretion phase, the alveolar epithelium undergoes pyroptosis, the resulting products are absorbed by granulocytes and tissue macrophages [6].

In this case, neutrophils and cytotoxic T cells, along with the formed cyto- and chemokines, join the process for protection lung tissue from the virus. During the fight against the virus, edema develops at the site of injury resulting in severe pulmonary pneumonia that causes acute respiratory distress syndrome and fibrosis. The age factor aggravates the pathological process, i.e. these changes listed are more likely to manifest themselves more pronounced in the elderly [7]. When the body immune response to the SARS-CoV-2 virus is insufficient, the virus enters the bloodstream and can damage other organs and cells that have receptors on their surfaces: intestines, kidneys, esophagus, heart, blood vessels, brain, bladder, etc.

It is also thought, that SARS-CoV-2 disease is a type of general viral vasculitis, and damage to the lungs in this disease is one different type of angiogenic edema. The distinctive feature of SARS-CoV-2 is the widespread involvement of the immune system during development of this pathogenesis, which leads to the elimination of SARS-CoV-2 in the early stages, but in the late stages of severe inflammation, stimulates severe or even fatal dysfunction of some organs. Thus, due to the stimulation of endogenous immunomodulators synthesis by COVID-19, severe forms of "cytokine storm" occur, which results in the loss of control of the inflammatory process and a significant deficiency of organs and systems [8]. In the early stages of the disease, the virus nsp1 and rp6 proteins inhibit the formation of interferon. Macrophages entering the site of inflammation continue to produce chemo attractants for single-nucleated cells (mononuclear cells), and thus their concentration increases rapidly, which stimulates the inflammatory process to the next stage, the "cytokine storm". At this stage, levels of inflammatory cytokines and hematotractants continue to increase dramatically, as interleukins, monocyte hematopoietic protein MCP-1, macrophage inflammatory protein MIP-1a, TGF, CCL2, CXCL10, TNF (CXCL9) increase sharply [9].

In severe cases of SARS-CoV-2 infection, there are significant changes in the acute phase of the blood, and at this stage, inflammation markers such as C-reactive protein, ferritin, ceruloplasmin, blood clotting factors, indicative serum enzymes indicate a lack of multiple organs [10]. In about 82% of cases of peripheral blood, leukopenia, thrombocytopenia and loss of eosinophils with lymphopenia are observed. For this reason, SARS infection is characterized by the appearance of significant immunopathological elements. Coronaviruses can damage both the upper and lower parts of the human respiratory system. Most of the clinical signs do not differ in multiple types of viruses, in severe cases the disease results in bronchitis, pneumonia and acute respiratory distress syndrome.

Viral respiratory infections stimulate the inflammatory process and promote the development of pathophysiological processes against the background of an excess of active forms of cytokines and oxygen and/or nitrogen. The main generator of ROS is mitochondria, the SARS-CoV-3b protein of the COVID virus and the non-structural protein 10 (nsp10) can change the course of processes in mitochondria [11]. SARS-CoV 3b may enter mitochondria, while nsp10 may interact specifically with the NADH 4L subunit and cytochromoxidase II. It has also been shown that genes encoding mitochondrial DNA in peripheral blood mononuclear cells, as well as genes sensitive to oxidative stress such as peroxiredoxin 1, activate the ferritin heavy-chain polypeptide gene. Oxidative stress increases the expression of 2D type of anti-inflammatory phospholipase A2, which reduces antiviral immunity. Interestingly, in humans, phospholipase A2 2D is naturally activated as ages [12].

In humans, there is also protein kinase, which is activated by mitogens from the destructive effects of the external environment, such as oxidative stress, accumulation of DNA damage, carcinogens and viruses. Phosphorylated activated mitogenic protein kinases were found in all SARS-CoV-infected cells. A number of studies confirm that there is a direct link between oxidative stress and congenital immune damage, and that this mechanism is one of the main causes of lung tissue damage in SARS-CoV-2. Thus, those who have a deletion of the ncf1 gene that stimulates the formation of ROS and do not have Toll-like receptor-4 (TLR4) which activates innate immunity, have a natural resistance to respiratory viruses, including SARS COVID virus.

This is explained by the fact that organisms with such changes in the body do not produce oxidized 1-palmitoyl-2-arachidoinyl-phosphatidyl choline, which stimulates the formation of cytokines by macrophages and activates damaging mechanisms. It is also known that 3CLpro protease of SARS-CoV induces apoptosis in human promonocytes by increasing the formation of ROS. Occurrence of oxidative stress and activation of transcription factor NF-KB can lead to severe lung damage. In vivo oxidative stress, 3CLpro activates NF-icB-factor but inhibits protein-1-dependent transcription, so ROS-induced transmission of 3CLpro-stimulated NF-KB signal may have played a leading role in the pathophysiology of SARS-CoV-2 infection [13]. This is because the activation of the phosphatidylinositol-3-kinase/protein kinase pathway by various viruses during latent or chronic infections allows infected cells to avoid apoptosis, which in turn contributes to the spread of the virus in the body.

The severity of SARS-CoV infection increases with age. This is explained by age-related changes in the immune system, the accumulation of oxidized products, and, conversely, the weakening of antioxidant defenses, and the consequent accumulation of mass OAF due to the violation of the oxidation-reduction balance. In the late stages, the redox-sensitive factor transcription factor NF-KB is activated, which is accompanied by the induction of inflammatory cytokines (IL-6, TNF-α), an increase in adhesion molecules. Oxidative stress triggered by SARS-CoV and NF-KB transmission by Toll receptors can further increase the reactivity of target cells, resulting in severe lung damage.

Age-related changes are more pronounced in SARS-CoV infections, especially in pandemics, where the number of deaths from SARSCoV-2 is less than 0.2% in a population under 60 and close to 10% over 80 years of age. Hypertension, diabetes, obesity, and other such type diseases increase the risk of death in this age group to 5%. At present, coronavirus infection unequivocally belongs to the group of pathologies caused by free radical reactions. Thus, after SARS-CoV enters the body, infiltration of macrophages, monocytes and neutrophils into the lung tissue begins, and due to the presence of the virus in the body, they start to actively form ROS. In fact, this mechanism, that is the conversion of oxygen into active forms serves for defense cells, it is self-defense, because ROS has a lethal effect on the virus & virus-infected cells. FAD-dependent NADPH-oxidase of mitochondria rapidly increases the number of ROS by transferring electrons to oxygen.

This condition is called “oxidative stress” because it leads to a tenfold increase in oxygen reactive forms. Naturally, ROS primarily serves to remove damaged, weak, functionally unnecessary cells in the injury zone. However, in the process of cleaning the damaged area, the activity of some relatively healthy cells which are closely adjacent to it, is impaired. In order to control the process, the body begins to produce anti-inflammatory cytokines, and while they increase in the blood, circulating neutrophyls can adhere to the site of injury and damage the pulmonary endothelium. Proteases of neutrophils & ROS that break down lung proteins and increase so rapidly, that they are thought to be key elements in SARS-CoV infection, which damage lung tissue. The aggressive reaction of neutrophils, as we have noted, is primarily directed against the infected cell, so the cytotoxic effect of neutrophils weakens as the number of cells infected with the virus decreases. However, when the process gets out of control and the virus is widespread in the body, acute respiratory distress syndrome occurs. As the damaged cells are destroyed by neutrophils, the patient’s blood and kidney secretions begin to increase the products of DNA degradation, as well as malon dialdehyde, keto- and hydroxycholesterol, formed by the peroxide oxidation of lipids. Depending on the degree of damage to the lungs, the breakdown products of protein (carbonyls) in the blood and urine increase.

Nitric oxide is added to the process of cleansing the body of the virus, which is accompanied by an increase in nitroguanosine. Deficiency of the antioxidant system leads to the fatal outcome of SARS-CoV infection. Thus, the increase in the expression of the heavy ferritine chain (FTH1) in SARS-CoV infection [14] indicates the need to strengthen the antioxidant system, because ferritine stores iron and prevents its formation in ROS by Fenton reactions, thus forming a very important antioxidant system. In SARS-CoV infection, there is also an increase in other antioxidant iron-binding proteins that limit the rate of ROS formation. Of course, in the progressive stage of SARS-CoV-2 infection, when the virus spreads rapidly in the body, the need for prooxidants, rather than antioxidants, increases. This is because ROS eliminates damaged cells along with the virus and prevents the spread of infection. For this reason, at this stage the concentration of proteins that play an antioxidant role in the body and regulate iron metabolism-haptoglobin, ferrin, transferrin and ceruloplasmin-decreases in the blood.

Naturally, the lack of the above-mentioned proteins, which prevent the cascade reactions of ROS formation during the recovery phase and are actively involved in the maintenance of innate immunity, can result in unpleasant complications for the body. Taking into account the information on the mechanism of development of SARS-CoV-2 in the literature on homeostasis disorders, it is advisable to pay attention to the inhibition of viral replication; reduction of hypoxia; elimination of drug poisoning and toxic, allergic consequences; antioxidant therapy to prevent the formation of ROS during the recovery phase; anti-

inflammatory therapy. This goal could be achieved through the administration of antioxidants with viral properties, as well as the use of antiviral drugs with antioxidant effects. However, the literature suggests that antioxidant therapy alone is less effective in SARS-CoV-2 infection, so treatment should focus on the use of drugs used in previous respiratory infections. For example, using superoxide dismutase mimics (metalloporphyrins, metallocorroles, Mn biliverdins, Mn cyclic polyamines, Mn salens, and metal oxides and salts) [15] and inducers of antioxidant protection, scientists have proposed substances that stop the development of the disease and increase the effect of each other in lower respiratory tract infections. To achieve this, it is possible to increase the expression of genes of antioxidant enzymes or the activity of the enzyme itself.

Antioxidants lead to a reduction in virus-induced nuclear factor NF-kB [16] and the interferon regulatory factor-3 (IRF-3) transcription factors [17], as well as cytokines and chemokines. It has also been suggested, that a "cytokine storm" must be prevented in order to control systemic inflammation. Despite the antiviral activity of cytokines, their overproduction during this infection has a stronger destructive effect on lung tissue than the virus itself. Interferons belong to the antiviral group, but interferons themselves belong to the cytokine class, which leads to additional activation of immune cells, which overshadows the use of these drugs in the case of SARS-CoV-2. For this reason, there is currently an active search for alternatives to interferon, and these drugs include antioxidants that provide enzymatic and non-enzymatic protection of the body [18]. One of the factors that increase the body's non-enzymatic antioxidant defenses is vitamin C, which can have an anti-inflammatory effect by rapidly reducing the formation of ROS.

Due to its antiviral activity, vitamin C also calms the "cytokine storm" in the body against the virus, and from this point of view, it is more suitable than interferon [19]. Interestingly, vitamin C can be used both alone and in combination with other drugs that have a synergistic effect with it. Thus, vitamin C with sulforaphane has a positive effect in the treatment of acute inflammatory diseases requiring artificial ventilation of the lungs [20,21]. Vitamin C is currently actively used in the treatment of SARS-CoV-2 in China, and this antioxidant has even been included in the ClinicalTrials.gov protocols. Thiol antioxidants, such as glutathione, are also involved in the cell's non-enzymatic defense system because they break down peroxide radicals during viral respiratory disease, weakening apoptosis and inhibiting viral replication [22]. *In vitro* analysis of the antiviral effects of 5 antioxidant components such as tocopherol, thiamine, pantothenic acid, pyridoxine, biotin and glutathione showed that most glutathione and pyridoxine were active, while thiamine, biotin and tocopherol also had a fairly high inhibitory effect. Unsaturated fatty acids omega-3 and omega-6, as well as vitamins E, A and D, and metal ions with variable valence are significantly higher in antioxidant and anti-inflammatory effects, so they are recommended for use in the treatment of SARS-CoV patients. Recent studies have found a strong link between vitamin D deficiency and COVID-19 infection in the elderly population in different countries [23].

In addition to the mucolytic effect of N-acetyl-L-cysteine, it can prevent the induction of anti-apoptosis and anti-inflammatory IL-6, IL-8 cytokines, and has a strong antiviral effect. Vitamin C and N-acetyl-cysteine are currently the most widely used antioxidants in lung damage [24]. The antiviral effects of some flavonoids are directly related to their inhibition of 3C-like proteases. Thus, the preparation of quercetin from the group of natural flavonoids was found to have a negative effect on the synthesis of viral RNA and the level of cytokines in the blood [25]. Studies have also shown significant antiviral activity of resveratrol and catrexin drugs from the group of natural polyphenols. These compounds have been shown to be effective against viral replication as they have delayed expression of viral proteins, ergo these small polar molecules with a fused ring structure, most of which belong to the polyphenols group, will be used in the future as SARS-CoV-2 antiviral drugs. Anti-inflammatory and antioxidant, anti-coronaviral effects of taurine, carnosine and 4-hydroxyproline from animal origin has been found [26]. Studies have shown that the enzyme branch of the antioxidant defense system can restore the damaged regulatory mechanisms of the respiratory system, as well as significantly reduce viral titers under the influence of antioxidant enzymes. For example, the main antioxidant enzyme that inactivates superoxide radicals is superoxide dismutase and catalase, which inactivates hydrogen peroxide.

Melatonin, which is rapidly absorbed, also has significant antioxidant properties. There are data in the literature on the inhibitory effect of melatonin on necrotic pyroptosis-programmed cell death caused by NLRP3-inflammation inhibition during SARS-CoV [27]. Studies have shown that melatonin and α-lipoic acid can significantly reduce the damaging effects of antiviral drugs. The antioxidant properties of melatonin are indirectly due to the activation of antioxidant enzymes in the body, which allows to increase the body's overall defenses. It is known that melatonin deficiency occurs with age, and this feature should be taken into account in the treatment of elderly SARS-CoV patients. The anti-stress effects of melatonin have also been confirmed, which has a positive effect in the COVID pandemic.

Another antioxidant, astaxanthin, has high anti-inflammatory activity because it reduces C-reactive

protein, the effects of interleukin-1 and a number of other inflammatory mediators of the respiratory tract [28]. Recently, information has been published on the use of a well-known antiseptic, leukomethylene (a reduced form of methylene oxide), approved by the World Health Organization for use in the treatment of a wide range of diseases, for the treatment of SARS-CoV-2 patients [29]. This substance along with vitamin C, N-acetylcysteine and α-lipoic acid, has a significant antioxidant effect, prevents the spread of viral RNA, leading to a weakening of inflammation and hypoxia.

In the treatment of SARS-CoV-2 infection, there is a need to eliminate toxic side effects arised by the use of antiviral drugs, with antioxidant drugs. It is known that the protection of biological structures from ROS is carried out by different antioxidant mechanisms, which are realized through different regulatory pathways. Therefore, from a pathogenetic point of view, in order to ensure synergism and drug accumulation, antioxidant drugs should be prescribed not in isolated form, but in a complex way, that stimulates both enzymatic and non-enzymatic defense, and this aspect is already reflected in the treatment of SARS-CoV-2 patients. Thus, according to the adopted protocol, prevention and treatment of SARS-CoV-2 patients is carried out through a "vitamin cocktail" containing vitamins D and C, methionine, zinc, quercetin. Such a combination of these components, which provide antioxidant protection, is expedient from both a prophylactic and therapeutic point of view.

The development of vaccines can be expected, but it is a time-consuming and costly process, additionally, vaccine injection should be avoided in some group of patients, such as in diseases accompanied by thrombosis, hypertonia and so on, because their vaccination leads to death or, at least - to undesirable complications. The rise in uncontrolled SARS-CoV-2 infections and deaths is prompting scientists around the world to think of new strategies that could reduce the secretion of anti-inflammatory cytokines ("cytokine storms"). Loss of control of the inflammatory response can lead to even more serious consequences than the effects of the virus, and often results in a number of vital conditions, including respiratory failure, which can be fatal. Therefore, one of the main goals of the current pandemic is to quell the "cytokine storm" that occurs as a consequence of oxidative stress. Drugs currently used for anti-cytokine therapy may have hepatotoxic effects [30,31]. Substances used as an alternative to them should be highly effective and have well-absorbed antioxidant properties. It is a known that in the other respiratory viral infections vitamin C, N-acetylcysteine and glycine, as well as melatonin, quercetin, astaxanthin, glutathione, fat-soluble vitamins, polyphenols, unsaturated fatty acids, and a number of other substances with high anti-inflammatory effects have positive effect; these substances used as an alternative to toxic drugs show effective antioxidant properties and are well-absorbed, ergo they can be the drugs of choice in SARS-CoV-2 treatment.

Conclusion

Since a cytokine storm induced by viral infections like SARS-CoV2 is the main cause of predicting the death of the patient healthy tissues damage, it is recommended to use in the inflammation alteration phase drugs that help reduce this process. This approach is also justified in the treatment of similar infections accompanied by a cytokine storm surge.

Conflict of Interest

The authors declare they have no conflict of interest to be disclosed.

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