



# Montelukast Drug May Improve COVID-19 Prognosis: A Review of Evidence

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With the lack of effective therapy, chemoprevention and vaccination, focusing on the immediate repurposing of existing drugs gives hope of curbing the pandemic. Interestingly, montelukast, a drug usually used in asthma, may be proposed as a potential adjuvant therapy in COVID-19. The aim of the present article was to review the properties of montelukast that could be beneficial in COVID-19. Ten experimentally supported properties were retrieved, either related to SARS-CoV-2 (antiviral properties, prevention of endotheliitis and of neurological disorders linked to SARS-CoV-2), and/or related to the host (improvement of atherogenic vascular inflammation, limitation of the ischemia/reperfusion phenomenon, improvement of respiratory symptoms), and/or related to serious COVID-19 outcomes (limitation of the cytokine storm, mitigation of acute respiratory distress syndrome), and/or related to tissue sequelae (antioxidant properties, anti-fibrosis effects). Based on gathered theoretical evidence, we argue that montelukast should be further tested to prevent and treat COVID-19 outcomes.

**Keywords:** coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, montelukast, lukasts, treatment, research

## INTRODUCTION

Coronaviruses are a large family of single-stranded RNA viruses, which infect animals and humans. Since December 2019, the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously 2019-nCoV) is spreading worldwide. The virus is primarily spread between people during close contact, most often *via* small droplets produced by coughing, sneezing, and talking. COVID-19 is characterized by fever, cough, severe pneumonia, RNAemia, combined with the incidence of ground-glass opacities, clot formation and endotheliitis, and a variety of clinical signs including fatigue, cardiac and neurological outcomes (Ahn et al., 2020). Of note, while the majority of cases result in only mild symptoms, some progress to acute respiratory distress syndrome (ARDS) possibly precipitated by significant increase in blood levels of cytokines and chemokines. This “cytokine storm”, reportedly due to angiotensin-converting enzyme-2 (ACE2) downregulation by SARS-CoV-2 (Bourgonje et al., 2020), triggers a proinflammatory environment which is strongly associated with severe tissue damages, contributing to ARDS and fatal outcomes of COVID-19 patients (Kimura et al., 2013).

As of June 2020, the COVID-19 pandemic has affected millions of people in 196 countries and left hundreds of thousands dead. With the lack of effective therapy, chemoprevention and vaccination, focusing on the immediate repurposing of existing drugs gives hope of curbing the pandemic. Interestingly, a recent *in silico* exploration identified montelukast (MK), from the Leukasts family (LKs; i.e. cysteinyl leukotriene receptors antagonists), among the top-scoring clinically-oriented drugs likely to inhibit SARS-CoV-2 main protease (Huynh et al., 2020). One retrospective study consistently found that older asthmatic outpatients receiving MK had fewer episodes of confirmed COVID-19 than those not using MK (Bozek and Winterstein, 2020). The aim of this article was to review the properties of LKs, especially of MK, that could be beneficial in COVID-19 and would deserve further dedicated studies.

## MONTELUKAST

MK works as a cysteinyl leukotriene (cysLT) receptor antagonist. Leukotrienes are inflammatory mediators produced by the immune system. They promote bronchoconstriction, inflammation, microvascular permeability, and mucus secretion in asthma and chronic obstructive pulmonary disease. Consequently, use of high-dose MK as an anti-inflammatory agent is effective in acute asthma (Wu et al., 2003). MK is mainly used as a complementary therapy in adults in addition to inhaled corticosteroids. The use of MK is also known to decrease the frequency and severity of wheezing after an upper respiratory tract infection caused by adenovirus, influenza, metapneumovirus or coronavirus (Brodie et al., 2015). Common side effects include diarrhea, nausea, vomiting, mild rashes, asymptomatic elevations in liver enzymes and fever. In 2019 and 2020, concerns for neuropsychiatric reactions were added to the

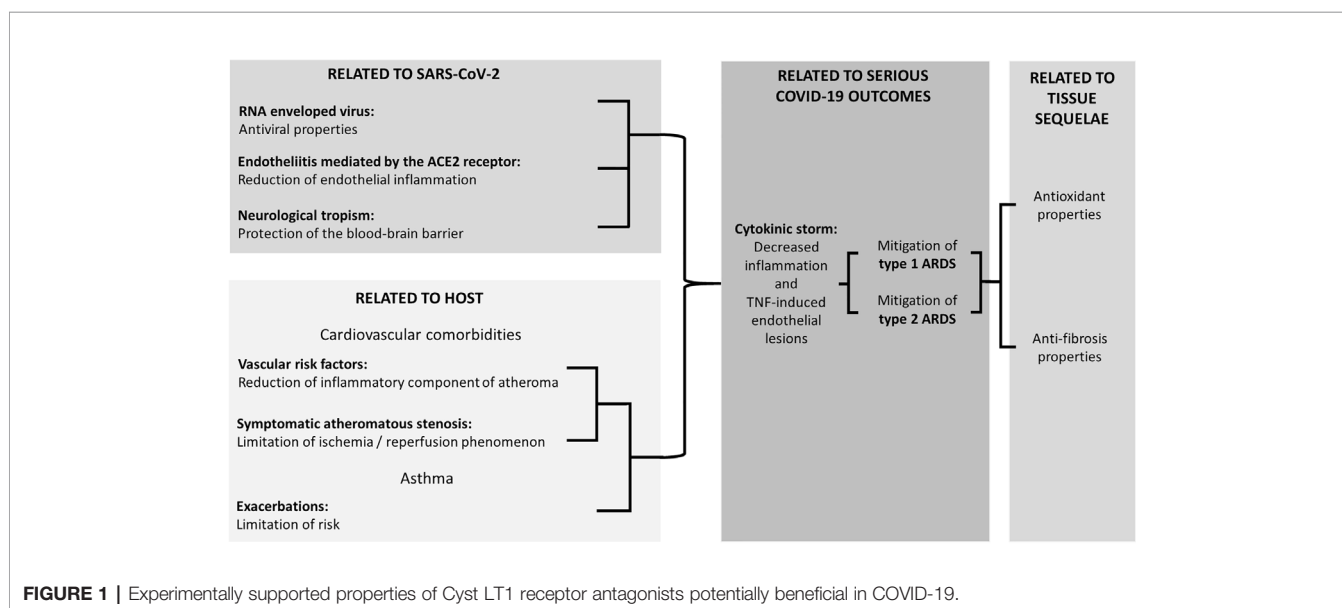
label in the UK and US where the most frequently suspected were nightmares, depression, insomnia, aggression, anxiety and abnormal behavior (Glockler-Lauf et al., 2019).

Apart from MK, LKs also include Zafirlukast (ZK) and pranlukast (PK). These three compounds may have properties of potential interest to treat COVID-19, the main ones of which are illustrated in **Figure 1** and described hereafter.

## PROPERTIES OF MK RELATED TO SARS-COV-2

### Antiviral Properties

Several antiviral properties of MK, potentially useful in COVID-19, have been described *in vitro* and *in vivo*, based on distinct mechanisms depending on the virus under investigation. For *Influenzae A* virus, an inhibition of the expression of the viral genome was observed with MK (Landeras-Bueno et al., 2016). For *flaviviridae*, in particular Zika virus, an irreversible and early inactivation of the virus was reported, probably due to some damage to the lipid membrane (Chen et al., 2020). Three distinct mechanisms were proposed to support the beneficial impact of MK on Zika virus: i) a direct antiviral action, ii) an antagonization of the cytokine storm, and iii) an inhibition of the vertical transmission by a MK-related neuroprotective effect on the brain of fetus. For the hepatitis C virus, MK induced a dose-dependent decrease in the levels of RNAs expressed, indicating an inhibition of viral replication (Ruiz et al., 2020). MK also attenuated the initial responses to respiratory syncytial virus (RSV) infection in neonate and adult mice, and reduced the consequences of RSV reinfection in mice initially infected as neonates (Han et al., 2010; Kloepper et al., 2011). Finally, in humans, Morita et al. (2017) have reported a decrease of almost 50% in the number of colds in younger boys aged 1 to 5.



**FIGURE 1** | Experimentally supported properties of Cyst LT1 receptor antagonists potentially beneficial in COVID-19.

## Endotheliitis Induced by SARS-CoV-2 Infection

SARS-CoV-2 interacts with the ACE2 receptors to infect the host (Bourgonje et al., 2020). This process is thought to promote the development of endotheliitis (Varga et al., 2020), a condition that may be responsible for the multiplicity of clinical signs observed in COVID-19. MK antagonizes the inflammatory cascade induced by angiotensin II in vascular smooth muscle cells (Mueller et al., 2010) and could therefore constitute a specific treatment for the inflammation induced by this condition (Fidan and Aydoğdu, 2020).

## Neurological Disorders Induced by SARS-CoV-2 Infection

Central nervous system disorders affect ca. 36.4% of patients with COVID-19 (Mao et al., 2020), mainly involving anosmia, dysgeusia, and headache. More serious manifestations such as seizures, delirium, encephalitis, and stroke have also been reported (Mao et al., 2020). LK limits the damage induced on the blood-brain barrier and has shown anti-convulsant properties in an experimental animal model of epilepsy (Lenz et al., 2014). Such protection of the blood-brain barrier could limit the occurrence and severity of brain damage (Zhou L. et al., 2019). It was also reported that MK improves fiber re-organization and long-term functional recovery after brain ischemia, enhancing recruitment and maturation of oligodendrocyte precursor cells (Gelosa et al., 2019). Additionally, a 6-week treatment with MK reduced neuroinflammation and elevated hippocampal neurogenesis through inhibition of the GPR17 receptor in younger and older rats (Marschallinger et al., 2015), with potential benefits for the prevention of manifestations such as delirium.

## PROPERTIES OF MK RELATED THE HOST

### Atherogenic Vascular Inflammation

It has been proposed that some severe complications of COVID-19 are mainly related to the host (Zhang et al., 2020). They are influenced by the age, gender and comorbidities, notably linked to preexisting inflammatory vascular and respiratory conditions. The cysLT are precisely strongly involved in the inflammatory phase of the atheromatous process although they are not used in this indication thus far. Antagonization of cysLT receptors greatly attenuates arterial spasm on human coronary arteries with atherosclerotic lesions, but it has no effect on healthy coronary arteries (Allen et al., 1993). A systematic review of the anti-atheromatous properties of MK in twenty-six animal and two human studies concluded that all studies supported the efficacy of LKs and MK on the atheromatous process (Hoxha et al., 2018). LKs could therefore reduce COVID-19 mortality in atheromatous patients, conferring a protection that would be (theoretically) proportional to the extent and severity of the atheromatous lesions (Almerie and Kerrigan, 2020).

### Ischemia/Reperfusion

The ischemia/reperfusion phenomenon results in downstream vascular lesions following reperfusion. In patients with severe

atheromatous disease, tissue hypoxia and hypoperfusion increase the risk of developing new endothelial lesions and ruptured atheroma plaque, inducing thrombosis and emboli. This may explain in part why COVID-19 is associated with an increased risk of arterial and venous thromboembolism, which affects approximately 30% of SARS-CoV-2-infected patients hospitalized in intensive care units (Klok et al., 2020). MK alleviates the ischemia/reperfusion phenomenon in animal models of intestinal anastomosis (Sayin et al., 2020), in skeletal muscles (Bilgiç et al., 2018), in the spinal cord (Korkmaz et al., 2015), and even following ovarian (Oral et al., 2011) or testicular torsion/distortion (Silay et al., 2014). A coronary stent coated with MK particles is being developed (Zamani et al., 2016).

### Asthma, Hyper-Reactivity Bronchitis, and Post-Infectious Cough

Asthma, for which LKs are usually prescribed, is a frequent and serious condition affecting 7%–8% of the population, though it is still under-diagnosed and under-treated (Deschildre, 2014). MK is effective against cough when it is an asthmatic equivalent, regardless of the functional respiratory parameters (Miwa et al., 2018). In contrast, MK has not shown any efficacy in chronic post-infectious cough (Wang et al., 2014), even though there was a high level of subjective improvement in the placebo group in this study (Wang et al., 2014). It would be of interest to examine MK on the mild symptomatic forms of COVID-19 respiratory damage (bronchospasms, cough, and chest pain).

## PROPERTIES OF MK RELATED TO COVID-19 SERIOUS OUTCOMES

### Cytokine Storm

The cytokine storm, corresponding to an unopposed generation of both pro-inflammatory and anti-inflammatory cytokines by the innate immune system, is responsible for most of the serious pulmonary complications of COVID-19 (Russell et al., 2020). The antagonist action of ZK on CysLT1 receptor protects the endothelium from inflammatory lesions induced by TNF- $\alpha$  (Zhou X. et al., 2019). By increasing IFN- $\gamma$  production and inhibiting the expression of cytokines such as IL-1 $\beta$ , IL-6, and IL-8, the inflammatory chain-reaction could be better controlled (Han et al., 2010). Clinically, MK is used to reduce drug-related cytokine reactions induced by daratumumab (Chari et al., 2018) and rituximab (Kotchetkov et al., 2020). In this indication, MK is associated with a marked decrease in frequency and intensity of cytokine reactions and this action seems to be strengthened by the addition of an anti-H1, namely rupatadine (Kotchetkov et al., 2020).

### Acute Respiratory Distress Syndrome

SARS-CoV-2-infected patients classically show mild symptoms that may gradually progress to more severe manifestations such as lethal ARDS. The type 1 ARDS is secondary to a direct alveolar inflammatory reaction, whereas the type 2 ARDS is secondary to systemic damage and occurs in the context of multi-visceral failure. To date, there is no effective chemotherapeutic treatment

for ARDS. The cornerstone of this condition remains the mechanical ventilation (Fan et al., 2018).

Regarding the type 1 ARDS, LK showed significant benefit on models induced by inhalation of irritant product like chlorine (Hamamoto et al., 2017) or pro-inflammatory lipids (Aquino-Junior et al., 2019), with a decrease in the intensity of the induced cytokine cascade and a lesser activation of neutrophils in the bronchoalveolar fluid. A similar effect was also reported in an animal model of malignant flu (Cardani et al., 2017).

Regarding the type 2 ARDS in an animal model of lung lesions induced by hepatic ischemia (Yeh et al., 2015) or hemorrhagic shock (Al-Amran et al., 2013), administration of LK resulted in a pulmonary reduction of neutrophil infiltration, lung inflammation, oxidative stress, and extent of lesions, along with a significant decrease in TNF- $\alpha$  and IL-6 cytokines in the pulmonary parenchyma and bronchoalveolar lavage.

## PROPERTIES OF MK RELATED TO TISSUE SEQUELAE

### Antioxidant Properties

An overproduction of reactive oxygen species (ROS) is crucial for viral replication and the subsequent virus-associated disease (Khomich et al., 2018). Experimental animal models of ARDS have shown enhanced ROS levels and disturbance of antioxidant defense during SARS-CoV infection (van den Brand et al., 2014). In cells infected with SARS-CoV, there was a greater amount of activated (phosphorylated) forms of all mitogen-activated protein kinase (MAPK) members (Khomich et al., 2018); i.e. a family of serine/threonine that are activated in response to environmental stresses including oxidative stress, DNA damage, carcinogenic stimuli and viral infections. Clinically, Shao et al. (2006) observed an upregulation of mitochondrial genes and genes responding to oxidative stress in peripheral blood mononuclear cells of convalescent SARS-CoV patients. Some of these genes, including PRDX1, FTH1 and FOS, are sensitive to oxidative stress and showed a remarkable elevation. These results support a role for oxidative stress during COVID-19. Importantly, protective effects of MK are not limited to inflammatory and microbial infectious attacks, but also include protection against chemotoxicity (bleomycin, cisplatin, doxorubicin, statin, paracetamol) (Hareedy et al., 2019) and radiotoxicity (Hormati et al., 2020) in animal experiments, which demonstrates some antioxidant properties resulting in increased mitochondrial mass and functionality, together with increased

intracellular cyclic adenosine 3, 5'-monophosphate (cAMP) level and activation of the Krebs cycle (Wang et al., 2019).

### Anti-Fibrosis Properties

Using MK may limit the residual extent of COVID-19 sequelae of pulmonary fibrosis, as for scar formation after lung surgery (Peng et al., 2017). MK regulates the extracellular remodeling matrix and inhibits the formation of fibrosis (Debelleix et al., 2018). This anti-fibrotic potential has been confirmed in an animal model of pulmonary fibrosis induced by bleomycin (Topaloğlu et al., 2018). Similarly, a recent meta-analysis confirmed in women that MK decreases the risk of retractile fibrosis after the placement of a silicone implant in breast reconstruction surgery (Wang et al., 2020).

## CONCLUSIONS

Although quantity is not quality, these 10 effects of MK may constitute as many synergistic and potentiating therapeutic possibilities in COVID-19. MK is a commonly used drug that does not require any prior cardiological or biological examination; it can be prescribed for pregnant women and frail older adults, and it shows a “comfortable” therapeutic range. Moreover, it could be all the more effective for patients with comorbidities such as diabetes, sleep apnea, smoking, obesity, or symptomatic atherosclerotic lesions. We support the conduct of clinical trials testing the effect of MK in COVID-19 patients from a variety of populations, while keeping in mind its adverse effects. Finally, it should also be emphasized that a potential massive use of MK in COVID-19 would risk depriving asthma patients of their treatment, which should also be anticipated.

## AUTHOR CONTRIBUTIONS

CA has full access to all of the data in the study, takes responsibility for the data, the analyses and interpretation and has the right to publish any and all data, separate and apart from the attitudes of the sponsors. All authors contributed to the article and approved the submitted version. Study concept and design: JB, J-MS, and CA. Drafting of the manuscript: JB and CA. Critical revision of the manuscript for important intellectual content: J-MS. Study supervision: CA.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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