

Review Article:

# An Update of Pharmacological and Non-pharmacological Therapies for COVID-19 Pandemic Trivia



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Article info:

Received: 09 May 2020

Accepted: 16 Jun 2020

Keywords:

COVID-19, SARS-CoV-2, SARS, MERS, Pandemic

## ABSTRACT

**Background:** The whole planet is facing one of the scariest pandemic situations in this era. On 11th February, 2020 the World Health Organization announced the name of an unknown disease as COVID-19, which is caused by the ssRNA virus SARS-CoV-2 (formally recognized as a sister of SARS-CoV and MERS-CoV). The epicenter of this disease is Wuhan, Hubei Province, China. COVID-19 can affect all age groups, but particularly affects immune compromised and aged persons with co-morbid conditions. It is highly contagious disease that involves mild to severe respiratory symptoms along with breathing difficulties.

**Objectives:** As SARS-CoV-2 is a new strain of  $\beta$ -coronavirus that spreads from animals to humans via an unknown intermediate host, no vaccines have been developed yet and only supportive treatment is given to the infected patients. The review paper highlights the pharmacological therapy as a supportive treatment given to the COVID-19 patients and non-pharmacological therapeutic approaches for the prevention.

**Methods:** Methods: Authors were surveyed and reviewed numerous articles, magazines, news papers, conference proceedings from different search engines and made the review successful.

**Results:** Some drugs of different categories are approved and prescribed to the patients and some others are still under investigation and have gone through clinical trials.

**Conclusion:** As no specific treatment or drugs for this disease have been developed till the date; therefore, social distancing, home quarantine, and proper healthy lifestyle management are the best current short-term options to avoid further spread of this pervasive virus.

**Citation** Goswami S, Pal N, Nath Mishra K, Singh P, Chegini Z, Pal Singh R. An Update of Pharmacological and Non-pharmacological Therapies for COVID-19 Pandemic Trivia. Pharmaceutical and Biomedical Research. 2020; 6 (Special Issue on COVID-19):27-36. [http://dx.doi.org/10.18502/pbr.v6i\(s1\).4399](http://dx.doi.org/10.18502/pbr.v6i(s1).4399)

**doi:** [http://dx.doi.org/10.18502/pbr.v6i\(s1\).4399](http://dx.doi.org/10.18502/pbr.v6i(s1).4399)

## Introduction

The current global pandemic is caused by a novel coronavirus, SARS-CoV-2, a member of the Coronaviridae family, and similar to SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (the Middle East Respiratory Syndrome Coronavirus), whose outbreaks were in 2003 and 2012, respectively [1, 2]. Last year in December, there was an outbreak of pneumonia of unknown origin in Wuhan, Hubei Province, China. The World Health Organization (WHO) announced this outbreak as a global pandemic on March, 11, 2020 [3]. Table 1 tabulates the taxonomic classification of this virus according to the National Center for Biotechnology Information Taxonomy Browser [4]. The Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) called it SARS-CoV-2, which causes the pandemic disease COVID-19.

As SARS-CoV-2 is a new strain of coronavirus and no vaccine or proper treatment is currently available, this review primarily focuses on the pharmacological along with non-pharmacological therapeutic approaches, which can be used as prophylactic measures in the current situation.

## Materials and Methods

The literature review has been successfully done by searching medical terms of “COVID-19”, “SARS-CoV-2”, “Coronaviridae”, “Zoonotic”, “Etiology”, “Transmission”, “Zinc ionophore”, “Replication”, “Mechanism of drugs” in online databases as well as search engines like Scopus, Google Scholar, PubMed, Publons, Elsevier, Springer and so on. Authors searched and reviewed more than 70 research articles, review papers, magazines, and newspapers. Then, they included 41 articles after reviewing the full-text, and the remaining 29 were excluded because of unauthentic, less reliable information (Figure 1).

**Table 1.** Taxonomical classification

Category	Coronaviruses
Realm	Riboviria
Order	Nidovirales
Suborder	Cornidovirinae
Family	Coronaviridae
Genus	Betacoronavirus
Subgenus	Sarbecovirus
Species	Severe acute respiratory syndrome coronavirus

## Etiology and contagion

SARS-CoV-2 is a single-stranded RNA virus with crown-shaped projections along with glycoprotein spikes in the envelope. This virus is mainly responsible for mild to severe acute respiratory or extra-respiratory manifestations. The common human coronaviruses of HCoV-OC43, HCoV-HKU1 ( $\beta$  coronavirus category), HCoV-229E, and HCoV-NL63 ( $\alpha$  coronavirus category) can cause the common cold, upper, and lower respiratory tract infection. The virus especially affects immune-compromised patients, elderly ( $\geq 60$  years old), and patients with co-morbid conditions like diabetes, cardiovascular diseases, and cancer, HIV/AIDS [6, 7]. Though the mortality rate is very low (approximately 2%-4%), but COVID-19 is a highly contagious disease [8]. SARS-CoV-2 is a zoonotic virus; it might be transmitted from bats and use ACE2 (Angiotensin Converting Enzyme 2), similar receptor as SARS-CoV, to infect humans via unknown intermediate carrier [9]. The transmission occurs through the contact of respiratory droplets of an infected person.

## Diagnosis

A rapid diagnostic test based on the host's antibody detection can be done by RT-PCR (real-time reverse transcriptase-polymerase chain reaction). Upper and lower respiratory tract specimens through nasopharyngeal and oropharyngeal swabs along with blood specimens can be taken for the identification of the virus [10].

## Clinical therapies

There is no definitive treatment for this pandemic disease to date. Only supportive pharmacological and non-pharmacological therapeutic measures and alternative herbal/traditional medicines can protect the patients from this homicidal virus.

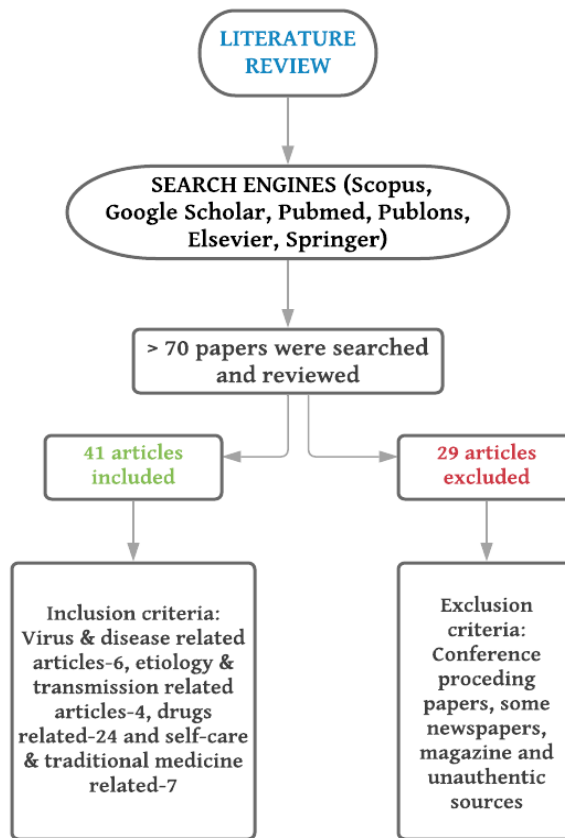


Figure 1. Flow diagram of the study

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### Pharmacological therapy

Some anti-viral and anti-malarial drugs are given to the patients in certain conditions by following proper therapeutic guidelines as supportive therapy. Besides these drugs, some antibiotics are also prescribed for empirical therapy. The medications that are given to the CO-

VID-19 patients are tabulated in Table 2. The possible pharmacological therapy is described as below:

### Hydroxychloroquine

Hydroxychloroquine is a derivative of chloroquine, an anti-malarial drug, which belongs to the 9-aminoquinoline

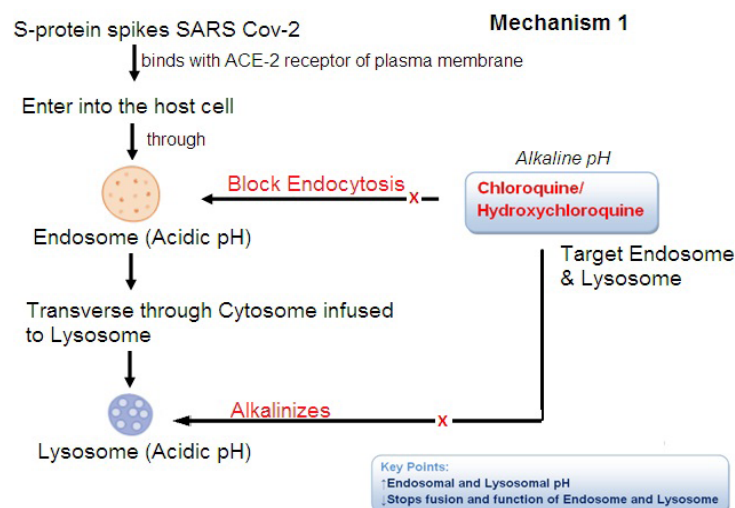
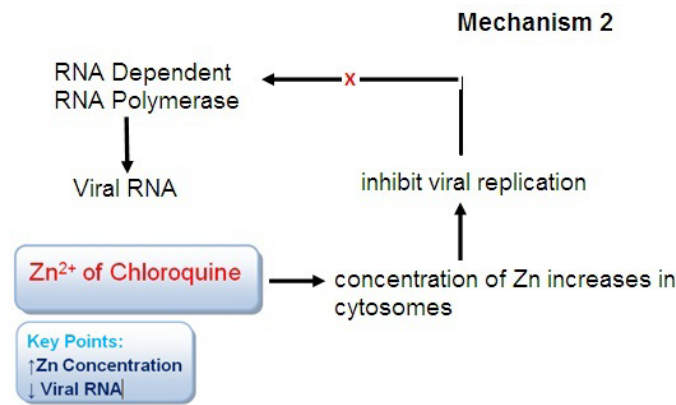


Figure 2. Hydroxychloroquine to stop endocytosis

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**Figure 3.** Hydroxychloroquine to inhibit viral replication

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category. This drug has immunomodulatory effects, i.e. used to treat rheumatoid arthritis and also effective in HIV and SARS as well [11-13]. Hydroxychloroquine shows its anti-viral actions against SARS-CoV-2 in three ways.

Mechanism 1: It stops endocytosis by alkalinizing vacuolar and lysosomal pH [14] (Figure 2).

Mechanism 2: Hydroxychloroquine is a zinc ( $Zn^{2+}$ ) ionophore and inhibits viral replication [15, 16] (Figure 3).

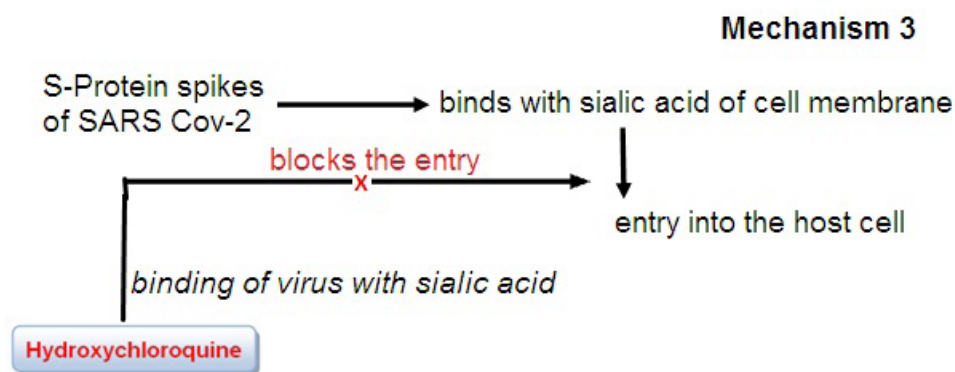
Mechanism 3: The drug binds with the sialic acid of the cell membrane and blocks the entry of the virus in the host cell [7, 18] (Figure 4). But the drug has an adverse effect also. The combination of hydroxychloroquine and azithromycin is very dangerous to patients with heart problems because it prolongs the QT interval leading to cardiac arrhythmia. Though Donald, Trump American President, publicized that the drug could be a ‘game-changer’ but US FDA warned to prescribe this drug because nearly 2 dozen patients passed away after taking the drug [19, 20].

**Lopinavir/Ritonavir**

These drugs are protease inhibitors approved by US-FDA for the treatment of HIV/AIDS. The combination of these drugs is used to increase the half-life of lopinavir. The drug cannot be given to pregnant ladies or patients with liver dysfunction or allergy. SARS-CoV-2 relies on 3-Chymotrypsin Like protease (3CLpro). These drugs inhibit the effect of 3CLpro, release in the host cell, and disrupting the viral replication [12, 21, 22].

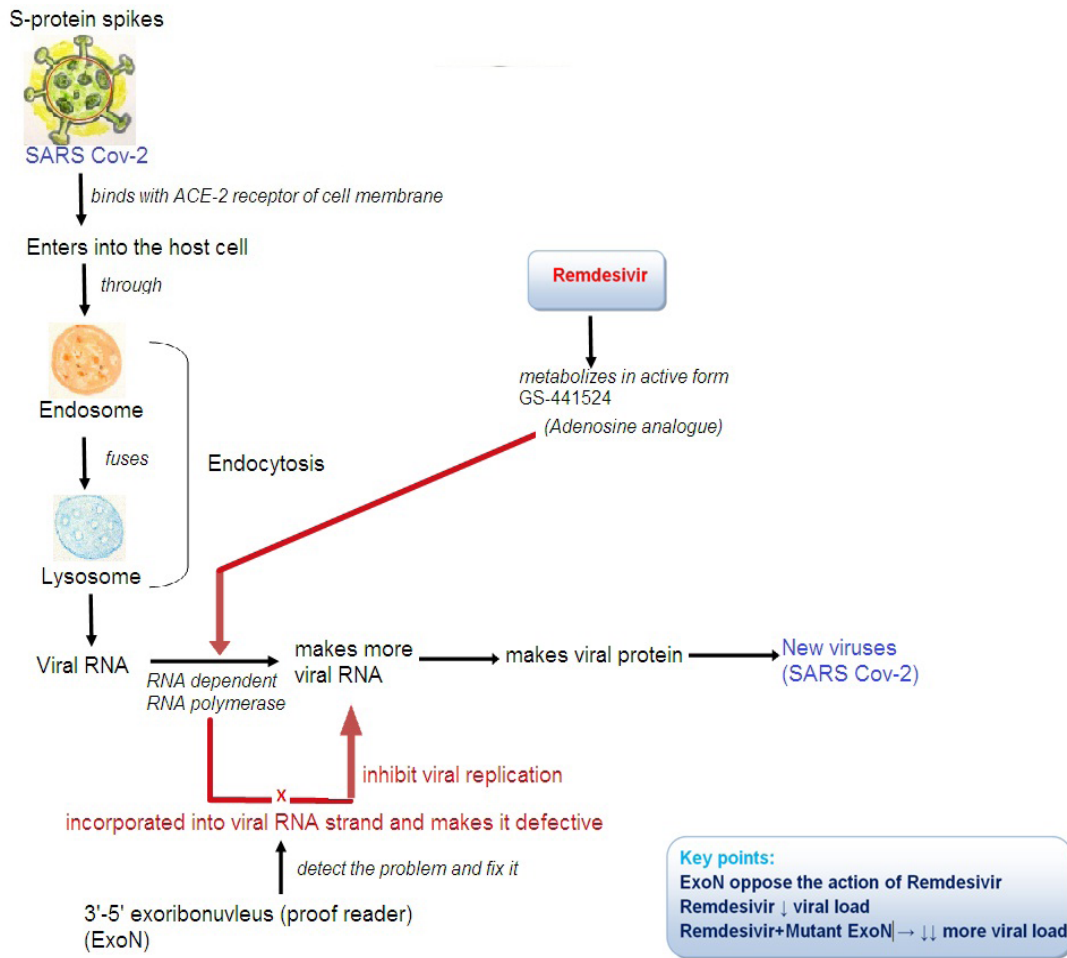
**Remdesivir**

The drug is an adenosine triphosphate analog used for the treatment for Ebola and is effective against SARS-CoV, MERS-CoV. It is also effective in in vitro studies of human respiratory epithelial cells. It metabolizes into its active form, GS-441524, which disrupts the Viral RNA production. But, there might be a probability of mutation of exoribonuclease for which remdesivir may be resistant to SARS-CoV-2 [23-26]. The mechanism of action of this drug is shown in Figure 5.



**Figure 4.** Hydroxychloroquine to block the entry of the virus

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**Figure 5.** Remdesivir to stop the process of viral RNA production

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### Favipiravir or avigan

A modified pyrazine analog is mainly developed for treating Japan flu. After ribosylation and phosphorylation, the active metabolic form (T-705-RTP) of favipiravir is incorporated into the nascent RNA strand and potentially inhibits RNA-dependent RNA-polymerase of viral RNA which prevents the replication and proliferation of viral genome. This drug is under investigation and concerns about clinical trials for SARS-CoV-2 infection [20, 27].

### Tocilizumab

The pathological examination of COVID-19 patients shows bilateral alveolar damage along with cytotoxic fibroblast exudate and decreases CD4 and CD8 T-cells resulting in the Cytokine Release Syndrome (CRS). CRS happens in most of COVID-19 patients. So, tocilizumab binds with transmembrane IL-6 Receptors (mIL6R) and soluble IL-6 Receptors (sIL-6R) and blocks the viral

signal transduction. This drug is under investigation for COVID-19 treatment [28-30].

### Oseltamivir

This neuraminidase inhibitor is used against influenza type-A viruses. It inhibits viral neuraminidase to stop spreading the infectious virus in the host cell [31].

### Acyclovir

Acyclovir, a nucleoside analog, mainly works against Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV). It terminates the viral chain and blocks the action of virus [9, 32].

### Famotidine

This Over the Counter (OTC) drug is a histamine receptor blocker that is used for the treatment of gastroesophageal disturbances. The drug blocks H<sub>2</sub> receptors

that release acid. The Chinese physicians observed that more than 6000 SARS-CoV-2 infected patients who intake famotidine in their previous medication history have a recovery rate better than those who did not take this medication. But, there is no idea how these drugs work against SARS-CoV-2. The research is going on the mechanism of this drug against COVID-19 [33, 34].

Recently, the Indian Council of Medical Research announced that 80% of patients remain asymptomatic and silent spreader and it is difficult to identify the infected patients [35]. The Union Health Ministry decided that the patients with no or mild symptoms must go to the self-isolation and have 24\*7 attendant direct contact with the doctor and hydroxychloroquine is prophylactic therapy for those patients. Among those asymptomatic patients, approximately 20% of cases turn severe and immediately seek medical help [36].

Moreover, one study published in the British Journal of Haematology has found that some Caucasian COVID-19 patients were suffered from abnormal micro clots in the lungs that led to their death. Patients with blood clots might develop the hypercoagulable state, ecchymosis and D-Dimer test coagulation factors appear abnormal. In this case, for the alleviation of hypercoagulation, the researchers from Hematology department of Peking Union Medical College Hospital suggest to use intravenous immunoglobulin which can be helpful in the inhibition of cytokine storm and low molecular weight heparin might be used to dissolve the micro clots and relief the patients from ecchymosis and other severe complications [37, 38].

## Results

### Herbal/Traditional medicine

Shuanghuanglian, a traditional Chinese medicine, which is a mixture of Weeping Forsythia (*Forsythia suspense*), Honeysuckle (*Lonicera*), Chinese skull cap (*Scutellaria baicalensis*) is used to treat the common cold, fever, sore throat and is characterized by anti-viral as well as antibiotic folkloric medication. This drug enhances the immunity power and investigation on Shuanghuanglian is in progress against SARS-CoV-2 [39, 40].

### Non-pharmacological Therapeutic approach

Therapeutic lifestyle modification consisting of both pharmacological and non-pharmacological approaches to prevent COVID-19 and should be part of all treatment plans for the patients with COVID-19 and their caregivers along with health care providers. The guidelines provided by the Ministry of AYUSH for self-care or as non-pharmacologic approaches during COVID-19 pandemic to boost immune power are [41]:

- Avoid dry mouth, drink lukewarm water regularly.
- Use spices like ginger, garlic, turmeric, coriander, and cumin for cooking because all these spices have the potential of boosting immunity.
- Take Chyawanprash 1 teaspoonful every day to restore vitality and stamina.
- Drink herbal tea with basil, ginger, black pepper. Methylxanthines present in tea, act as a bronchodilator which is useful in respiratory diseases.

**Table 2.** Potent drugs given to the patients (approved or under investigation)

Drugs	Uses	Category	Effect in COVID-19
Hydroxychloroquine [11-13, 20]	Malaria, HIV, SARS, Rheumatoid arthritis	9-Aminoquinoline	It blocks the ability of viruses for replication by boosting up its pH and turns the acidic environment of endosomes and lysosomes in basic.
Lopinavir/Ritonavir [12, 21, 22]	HIV/AIDS	Protease inhibitor	Inhibits the effect of 3-Chymotrypsin Like protease (3CLpro) and disrupting the ability of viral replication
Remdesivir [9, 11, 26]	Ebola, SARS, MERS	Adenosine triphosphate analogue	Disrupts the viral RNA production.
Favipiravir or avigan [9, 11, 20]	Japan flu	Modified pyrazine analog	Active metabolite T-705-RTP prevents the replication and proliferation of viral genome.
Tocilizumab [12, 28, 30]	Rheumatoid arthritis	Interleukin-6 (IL-6) blocker (Immunosuppressant)	Blocks the viral signal transduction
Oseltamivir [9, 12]	Influenza viruses type A	Neuraminidase inhibitor	It inhibits viral neuraminidase to stop spreading the infectious virus in the host cell.
Acyclovir [12, 32]	HSV, VZV	Nucleotide analog	It terminates the viral chain and ineffective the action of the virus.

- Take golden milk made by hot milk and turmeric once or twice every day to promote the immunity system.
- Do Pratimarsha nasya (apply sesame/coconut oil both nostrils) regularly.
- Daily practice Yoga, Pranayama (Kumbhaka i.e. retention of breath for 10 s).
- Inhale steam with mint, caraway seeds.
- Do gargle with clove powder and honey in case of cough, sore throat.
- Frequently wash hands with soap and water for 20 s or rub hands with ethanol-based sanitizer.

## Discussion

The whole review reveals that non-pharmacological therapeutic approaches and lifestyle modification can surely boost the body's immune system to keep it fighting fit which is the need of the hour. Pranayama heals our body, reduces stress levels. Also, regular yogic breathing practices prolong inhalation and exhalation, which provides more oxygen into our blood and expels toxins or vitiated air out of the body. A stronger immune system fights against any kind of infection of the body. As there is no definitive medicine or vaccine available for the treatment of COVID-19 yet, some antiviral drugs such as chloroquine/hydroxychloroquine, lopinavir/ritonavir, remdesivir, etc. are used as a supportive and prophylactic treatment. The mechanisms of these drugs' actions against SARS-CoV-2 have already been presented in Table 2. Some other drugs are under pre-clinical and clinical trials. COVID-19 and SARS-CoV-2 are just the 'tip of the iceberg' which needs further research.

## Conclusion

prevention is a better option than a cure. Social distancing and self-quarantine is the only current best option for preventing this global pandemic disease. Since the disease spreads via respiratory droplets, so maintaining social distance (minimum distance 2 m) is a good way for prevention. During coughing, sneezing, use disposable tissues, flex elbow. By maintaining proper hygiene, good eating habits and healthy lifestyle management can surely help for the prevention of this homicidal disease until the invention of vaccines or medicines.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

### Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

### Authors' contributions

Conceptualization: Shambaditya Goswami; Design: Nikita Pal; Data collection: Kushal Nath Mishra; The tables and figures of the paper and data analysis: Prashant Singh.

### Conflict of interest

The authors declare no conflict of interest.

### Acknowledgments

The authors are thankful to the Management and Director of NIMS University for their guidance and valuable suggestions to complete this article.

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