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# Widely available lysosomotropic agents should be considered as a potential therapy for COVID-19

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## Abstract

While the COVID-19 pandemic advances, the scientific community struggles in the search for treatments. Several improvements have been made, including the discovery of clinical efficacy of chloroquine (CQ) in COVID-19 patients, but the effective treatment protocols are still missing. In order to find novel treatment options many scientists utilize the *in silico* approach to identify compounds that could interfere with the key molecules involved in entrance, replication, or dissemination of the SARS-CoV-2. However, most of the identified molecules are currently not available as pharmacological agents, and assessing their safety and efficacy could take many months. Here, we took a different approach based on the proposed pharmacodynamic model of CQ in COVID-19. The main mechanism of action responsible for the favourable outcome of COVID-19 patients treated with CQ seems to be related to pH modulation-mediated effect on the endolysosomal trafficking, a characteristic of chemical compounds often called lysosomotropic agents because of the physico-chemical properties that enable them to passively diffuse through the endosomal membrane and undergo protonation-based trapping in the lumen of the acidic vesicles. In this review, we discuss lysosomotropic drugs that are already in clinical use and are characterized by good safety profiles, low cost, and wide availability. We emphasize that some of these drugs, in particular azithromycin and other macrolide antibiotics, indomethacin and some other non-steroidal anti-inflammatory drugs, proton pump inhibitors, and fluoxetine could provide additional therapeutic benefits in addition to the potential antiviral effect that still has to be confirmed by well-controlled clinical trials. As some of these drugs, mostly antibiotics, were already empirically used in the treatment of COVID-19, we encourage our colleagues all over the world to publish patient data so potential efficacy of lysosomotropic agents can be evaluated in the clinical context and rapidly implemented in the therapeutic protocols if the beneficial effect on clinical outcome is observed.

## Introduction

The main objective of every virus is to hijack the intracellular machinery of the host cell for genome replication and assembly. To achieve this, the virus first has to bypass the cellular membrane barrier. The structure of some viruses enables a direct fusion at the plasma membrane after the recognition of the binding site[1]. However, most of the enveloped viruses depend on the endocytic pathway prior to fusion with the host cell[2]. Once the endocytosis has been initiated, survival and replication of the virus depend on the successful delivery of the viral nucleocapsid into the right intracellular department, as different viral families target distinct compartments as primary replication sites[3]. Moreover, in order to survive, the virus has to escape from the endosomal compartment silently, without triggering the cellular defense mechanisms[4]. As a result, viral evolution produced highly complex escape strategies relying on different cues of endosomal maturation and trafficking[5]. Establishment of an acidic

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endosomal lumen is the key requirement for normal functioning of the endocytic pathway[6] so pH sensing evolved as one of the fundamental strategies viruses use for endosomal maturation monitoring[7]. Two important sensing strategies are used by most viruses for induction of the membrane fusion mechanisms: direct pH sensing mediated by a conformational change of the envelope glycoproteins and endosomal protease-mediated proteolytic cleavage[7]. From a pharmacological perspective, this makes endosomal pH an attractive drug target. Neutralization of the endosomal pH obstructs endosomal trafficking, impedes sorting mechanisms, and inhibits the activity of the endosomal proteases[6]. As a consequence, pharmacological modulation of the endolysosomal pH could prevent viral fusion, and impair the formation of the viral replication complexes. Moreover, as pH modulation is important for regulation of the exocytosis, vesicular pH modulation could also affect viral dissemination[8]. Endosomal trafficking is necessary for normal cellular functioning, so long-term disruption of endosomal function could lead to considerable pathophysiological consequences[9]. Moreover, the infectivity of some viruses that use alternative strategies to enter the cell could even be increased by the pH-mediated inhibition of the endosomal pathway[10]. For this reason, most of the antiviral drug development strategies focused on more specific fusion mechanisms rather than the general inhibition of the endocytosis pathway. However, short-term inhibition of the endocytosis could be a viable strategy for the management of viral infections with no alternative treatment options such as COVID-19. Recent evidence suggests chloroquine (CQ) and hydroxychloroquine (HCQ) might be effective therapeutic strategies for COVID-19[11–14]. Although the exact mechanism of action responsible for antiviral activity of both CQ and HCQ remains to be fully understood, the elevation of lysosomal pH seems to play a key role[14]. This is in concordance with previous findings as proteolytic processing of the glycoprotein S by lysosomal proteases seems to be necessary for the fusion of coronavirus with the host cell[2]. Moreover, treatment of cells with glycoprotein S, the main protein responsible for viral fusion of SARS-CoV and SARS-CoV-2, resulted in translocation of the main viral receptor, angiotensin-converting enzyme 2 (ACE-2), to endosomal vesicles[15]. Furthermore, the same effect was demonstrated for spike-bearing pseudoviruses, emphasizing the importance of glycoprotein S for viral fusion[15]. It is important to mention that although many groups demonstrated that SARS-CoV enters the cells by receptor-mediated, pH-sensitive endocytosis[15], some groups reported that the viral fusion might also occur by pH-independent direct fusion with the plasma membrane[16]. Although the exact mechanism responsible for the entrance of SARS-CoV-2 in the host cell remains to be elucidated, we believe data from clinical trials on CQ and HCQ speaks in favor of the importance of pH-dependent endocytosis, and that other widely available pharmacological agents with lysosomotropic properties might also demonstrate clinical effectiveness in the treatment of COVID-19. In this review, we discuss commonly used pharmacological agents in context of their lysosomotropic effects and pH modulation-mediated interaction with cytoplasmic vesicle trafficking. Even though more than 260 000 people have been diagnosed with COVID-19 as of the 20$^{th}$ of March, organized clinical data that would enable us to evaluate potential antiviral effects of the drugs discussed below is unavailable at the moment. We use this opportunity to strongly appeal to our colleagues in possession of such data to evaluate possible benefits of these drugs, as they might offer us a new hope both in prevention and treatment of this devastating disease.

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## A brief introduction to the concept of lysosomotropism in pharmacology

The concept of lysosomotropism was first introduced by De Duve et al. in 1974[17]. The term was originally proposed for all substances taken up by lysosomes, regardless of their chemical structure or mechanism of action. Interestingly, the importance of the potential antiviral properties of lysosomotropic agents was emphasized even in the original publication[17]. Moreover, some of the original concepts of lysosomotropism, such as the possibility to make virtually any substance lysosomotropic by suitable coupling with an appropriate chemical carrier are now considered to be common principles in drug design. In general, most of the substances with weakly basic and lipophilic properties are believed to demonstrate lysosomotropism to some extent. These properties enable lysosomotropic drugs to passively diffuse through the endosomal membrane and undergo protonation-based trapping in the lumen of the acidic vesicle. From a chemical standpoint, most of the drugs that demonstrate lysosomotropic properties are cationic substances that usually belong to the group of primary, secondary, or tertiary amines, and from a pharmacological point of view these compounds are often described by very large volumes of distribution and long residual effects[18]. For a deeper understanding of the current concept of lysosomotropism we point the interested readers to the informative review by Marceau et al.[18]. Antimalarial drugs, such as CQ that recently demonstrated clinical efficacy in the treatment of COVID-19[11] are often referred to as classic lysosomotropic agents because their primary mechanism of action relies on their lysosomotropic properties. The CQ works by sequestration in the digestive vacuoles that resemble endolysosomal compartments and increasing their pH to stop the nutrient supply[18]. Another classic example are drugs used for the treatment of tuberculosis where the therapeutic effect of the drug is based on its delivery to the site of mycobacterial replication[18]. However, apart from the drugs that are well known lysosomotropic substances, many pharmacological agents from other therapeutic classes belong to this group of chemicals based on both their physico-chemical properties and the effect on endolysosomal function *in vitro* and *in vivo*. We suggest these drugs should be examined in the context of their potential use in COVID-19 treatment protocols as most of them could potentially be used for targeting both viral replication and dissemination and symptoms of the disease. In further text, we discuss lysosomotropic agents belonging to different groups of drugs and their potential use in the treatment of COVID-19. As many pharmacological agents have shown lysosomotropic properties both *in vitro* and *in vivo*, here we focused only on drugs that satisfied several criteria we considered important in this context: existing evidence of lysosomotropic action, good safety profile of the drug, wide availability, low cost, and additional therapeutic benefits apart from the potential preventive and therapeutic antiviral effect.

## Antibiotics

Initial reports have shown that more than 90% of patients with COVID-19 received antibiotics[19], however the reports on how the outcome of the patients depends on the use of different antibiotics are scarce. Several groups of antibiotics are known to be lysosomotropic, however the effect is most consistently observed for macrolides. Therefore, here we want to draw attention to macrolides as a potentially effective group of antibiotics in cases of COVID-19 as numerous studies have shown that macrolides possess anti-inflammatory, antibacterial and antiviral properties. Anti-inflammatory effects[20] are of particular interest as it has been suggested that a cytokine storm plays a central role in the development of ARDS after a high concentration of proinflammatory interleukins has been measured in the blood of deceased

patients[21]. Another reason to consider macrolides is their antiviral effect, particularly described for, but not limited to clarithromycin, bafilomycin, erythromycin, azithromycin[22,23]. Although the effects of macrolides on the expression of cytokines and membrane receptors contribute to the antiviral effects, the exact mechanism is still unknown[22,23]. Since it has been described by several authors that macrolides can affect lysosomal trafficking and lysosomal pH[24,25], here we hypothesise that this could be one of several mechanisms of antiviral activity of macrolides, especially interesting in COVID-19. Although the antiviral effects of macrolides are known for a long time, the use of these drugs in patients didn't yield groundbreaking results[22,26]. Nevertheless, a recent clinical trial proved the effectiveness of azithromycin in combination with HCQ[27], providing additional evidence for our hypothesis. Considering everything aforementioned and a recent *in silico* finding that clarithromycin and erythromycin could have a direct antiviral effect by interfering with COVID-19 protease [28], macrolides should be further investigated as a treatment option.

**Non-steroidal anti-inflammatory drugs (NSAID)**

The safety of NSAIDs in patients with COVID-19 has been debated ever since the discovery that ACE-2 is an entry receptor for SARS-CoV-2[29]. Fang et al. have hypothesized that ibuprofen increases the risk of developing a severe and fatal COVID-19 since it is known that it can increase the expression of ACE-2 receptors[30]. However, this still hasn't been supported by any clinical study and can not be confirmed *post hoc* with the current common practice of not making raw patient data available (Homolak & Kodvanj, *submitted commentary*). Nevertheless, taking into account the above-mentioned connection of endosomal trafficking and viral replication, NSAIDs could provide additional benefits in the treatment of COVID-19 as a result of their inhibitory effect on the autophagic flux[31]. Indomethacin is especially interesting in this context. Several studies have shown that indomethacin can increase the pH of lysosomes[31,32]. Moreover, some results suggest indomethacin can block viral RNA synthesis independently of the effect on cyclooxygenase inhibition and this effect was confirmed both *in vitro* and *in vivo* on canine coronavirus-infected dogs[33,34].In conclusion, at this point, there are not enough studies to demystify the potential role of NSAIDs in COVID-19, however, in addition to standard anti-inflammatory and antipyretic properties other factors should be taken into account such as possible effect on the expression of ACE-2, interference with the autophagic flux and possible direct antiviral activity. We believe more attention should be directed towards these potential effects and structured clinical data should be collected in order to examine if some NSAIDs should be considered better than others for this indication.

**Proton pump inhibitors (PPI)**

To alleviate the side effects of NSAIDs, proton pump inhibitors (PPI) are often concomitantly given. It is important to note that PPIs can inhibit V-ATP-ase, the enzyme responsible for maintaining pH in endosomes. As a consequence, PPIs can induce cytosolic acidification and lysosomal and endosomal alkalinization[35,36]. As discussed above, this effect could be beneficial in patients suffering from COVID-19. In the context of direct and indirect antiviral effect of indomethacin discussed before, and its well-known gastrointestinal side effects, a combination of indomethacin and PPIs should be further investigated as a potential therapeutic strategy in COVID-19. Additionally, ACE-2 that acts as a primary receptor for SARS-CoV-2 host cell entry is a well known intestinal transporter involved in amino acid absorption throughout the human small intestine[37], and gastrointestinal symptoms are

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reported to be a part of the clinical presentation of COVID-19[38,39], therefore targeting gastrointestinal system could potentially provide dual benefit as lysosomotropic agents could provide symptomatic relief and reduce viral dissemination. The possibility that fecal-oral transmission route is involved in spread of the virus in combination with recent findings that viral RNA remained positive in the feces even after negative conversion of the viral RNA in the respiratory system, further supports the idea that lysosomotropic agents that primarily target gastrointestinal system should be considered as part of the therapy for COVID-19[38].

**Selective serotonin reuptake inhibitors (SSRI)**

Many central nervous system drugs demonstrate lysosomotropic properties. Some lysosomotropic compounds often used in experimental work regarding endolysosomal trafficking and function include tricyclic antidepressants imipramine and amitriptyline, antipsychotic chlorpromazine, and SSRI fluoxetine[40]. If further research provides clinical evidence for the antiviral effect of fluoxetine it could be considered as part of the solution in addition to virtual psychotherapy for quarantine-induced anxiety. This might be more important than it seems, as findings published after the previous epidemic of SARS suggest psychological effects of quarantine are underestimated[41–43] and rapid response of the psychologists and psychiatrists during the ongoing epidemic confirms early intervention is important[44,45]. Moreover, maximal compliance is needed to implement successful quarantine and social isolation measures, and considering the information in the global media, anxiolysis is more important than ever if we want to stop the spread of the virus.

**Conclusion**

In conclusion, many pharmacological agents that are widely used in clinical practice demonstrate lysosomotropic properties both *in vitro* and *in vivo*, and should thus be considered as potential therapeutic agents for COVID-19 in light of the recent findings on clinical efficacy of CQ. Most of the drugs discussed in the text have great safety profiles, low cost, and are widely available which makes them interesting in the context of rapidly advancing pandemic we are witnessing. Some of these drugs were probably already empirically used in the treatment of COVID-19, so we use this opportunity to encourage our colleagues all over the world to publish patient data and evaluate the potential effect of the drugs discussed in the text. As we are still lacking the effective treatment strategies for COVID-19, repurposing of drugs based on their lysosomotropic effect could provide us with additional preventive and therapeutic options we desperately need.

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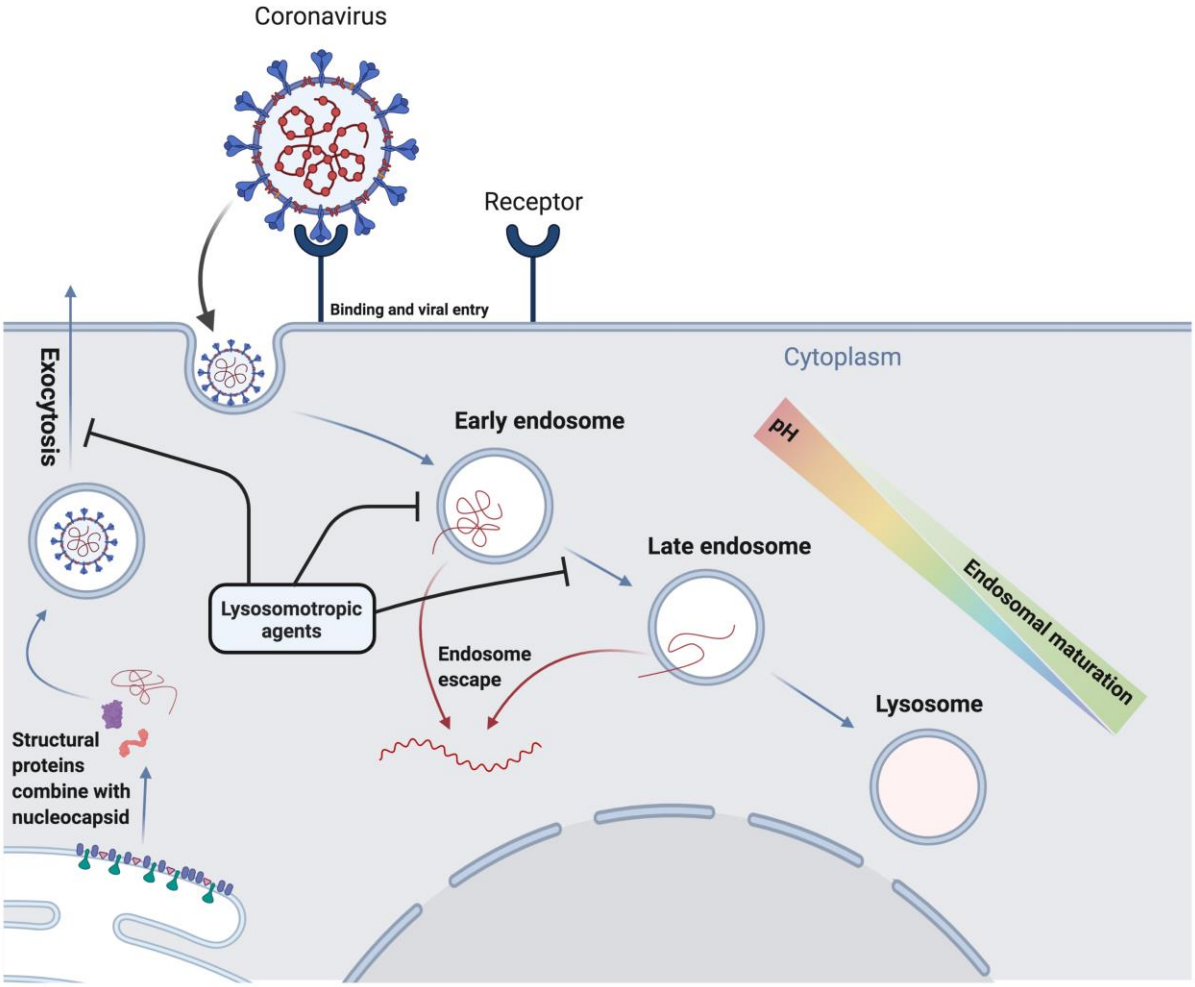


**Figure 1. Possible interaction of lysosomotropic agents with the replication cycle of SARS-CoV2 in a cell.** Lysosomotropic drugs, such as chloroquine, have the ability to interfere with endosomal trafficking, affecting both endosomal maturation and exocytotic pathways. Taking into consideration the dependence of viral replication on the normal functioning of endocytic trafficking, commonly used pharmacological agents that demonstrate lysosomotropic properties should be examined as a possible therapeutic option for the treatment of COVID-19.