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BIOENGINEERING

Research on repurposed antivirals currently available in Colombia as treatment alternatives for COVID-19

BIOINGENIERÍA

Investigaciones en reutilización de antivirales actualmente disponibles en Colombia como alternativas de tratamiento para el COVID-19

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Abstract

The coronavirus disease 2019 (COVID-19) was declared as pandemic on March 2020 by the World Health Organization. This respiratory disease is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and current efforts are focused in finding pharmaceutical alternatives and vaccines for both, preventing and treating the infected patients around the world. After quarantine and lockdown periods, the treatment of the disease is still limited to symptomatology management and remission to critical care units of the most severe cases. America accumulate the highest number of cases and casualties and the increased pressure over the economy led to the relaxing of mitigation measures. Several clinical trials involving antivirals have been conducted as available alternatives on the short term to face the increasing rate of contagions while experimental vaccines are properly developed and tested. Scientific literature refers a set of FDA approved drugs as repurposed compounds with potential action on the viral mechanism of SARS-CoV-2. In Colombia some of those substances are currently commercialized as antivirals and antiparasitic over-the-counter drugs, while other drugs also in the panorama are unavailable but potentially accessible in the short term for treating the COVID-19 in Colombia, until a massive vaccination campaign can be deployed in the country.

Keywords: *Antiviral, Bibliometric analysis, COVID-19, SARS-CoV-2, Molecular docking.*

Resumen

La enfermedad del coronavirus 2019 (COVID-19) fue declarada pandemia en marzo de 2020 por la Organización Mundial de la Salud. Esta enfermedad respiratoria es causada por el nuevo síndrome respiratorio agudo severo coronavirus 2 (SARS-CoV-2) y los esfuerzos actuales se centran en encontrar alternativas farmacéuticas y vacunas para ambos, prevenir y tratar a los pacientes infectados en todo el mundo. Después de los períodos de cuarentena, el tratamiento de la enfermedad aún se limita al manejo de la sintomatología y la remisión a las unidades de cuidados críticos de los casos más graves. América acumula el mayor número de casos y bajas y el aumento de la presión sobre la economía llevó a relajar las medidas de mitigación. Se han realizado varios ensayos clínicos con antivirales como alternativas disponibles a corto plazo para hacer frente a la creciente tasa de contagios, mientras las vacunas experimentales se desarrollan y prueban adecuadamente. La literatura científica hace referencia a un conjunto de medicamentos aprobados por la FDA como compuestos reutilizados con acción potencial sobre el mecanismo viral del SARS-CoV-2. En Colombia algunas de esas sustancias se comercializan actualmente como antivirales y antiparasitarios de venta libre, mientras que otros medicamentos también en el panorama no están disponibles, pero son potencialmente accesibles en el corto plazo para el tratamiento del COVID-19 en Colombia, hasta que una campaña de vacunación masiva se puede desplegar en el país.

Palabras Clave: *Acoplamiento molecular, Antiviral, Análisis bibliométrico, COVID-19, SARS-CoV-2..*

1. Introduction

In December 2019, several cases of atypical pneumonia were reported in the Chinese city of Wuhan. This disease was classified as a Severe Acute Respiratory Syndrome (SARS) caused by a novel coronavirus identified as SARS-CoV-2. Later, the associated disease was named as COVID-19 (Coronavirus disease 2019) and it was classified as a pandemic by the World Health Organization (WHO) on 11th March 2020. COVID-19 spread globally especially due to intense traffic of travelers between Europe, Asia and America.

The virus causing the COVID-19, i.e. the SARS-CoV-2, belongs to Coronaviridae family and β-coronavirus family as other viruses related to respiratory diseases like the SARS-CoV and MERS-CoV, which previously caused outbreaks in Asia (2002-2003) and Middle East (2012-2013), respectively. The genome of SARS-CoV-2 is a single-stranded RNA of 29 kb codifying 9860 amino acids. The infection mechanism of SARS-CoV-2 may occur via either angiotensin-converting enzyme 2 (ACE2) receptor or endocytosis [(1)]. The viral RNA is liberated in the cell followed by intracellular translation of polypeptides and proteins necessary for virus replication. Further proteolysis lead to proteins production as the case of the RNA-dependent RNA polymerases (RdRp) required for viral RNA replication, transcription and translation. The viral proteins are processed in the Endoplasmic Reticulum and Golgi apparatus and new viruses are assembled. Finally, viruses are released via exocytosis [(2)].

The respiratory disease caused by the SARS-CoV-2 shows the usual behavior of other respiratory syndromes in most countries. About 80% of the patients require ambulatory management, and approximately 5% require attention in high-dependency units [(3)]. During the course of the disease, dry cough is the prevalent symptom in 68% of the patients, associated with odynophagia and rarely nasal congestion (1.7%) [(3,4)]. Since COVID-19 is consequence of an infectious process, most patients (88%) present fever, which might precede the respiratory symptoms or occur during hospitalization [(3)]. Moreover, several studies have shown the frequent self-medication of Colombian population [(5–7)], self-medication with some over-

the-counter drugs like paracetamol (acetaminophen) and non-steroidal anti-inflammatories might mask the symptoms, hence previous medication intake must be questioned at admission to the emergency department. It is clear that fatigue and dyspnea increase during the course of the disease and, in particular cases (~5%), diarrhea occur as associated symptom occurs, which is particularly challenging for an appropriated anamnesis [3,4]. Furthermore, the presence of comorbidities, either primary or acquired immunodeficiency and respiratory tract diseases, such as chronic obstructive pulmonary disease and asthma, predispose to more severe manifestations with shorter time of evolution and considerably higher mortality rate [4].

Although research in the field is advancing rapidly, and vaccines under development are projected to reach the market during 2021, the approval, production and distribution might take several months. The forecasts suggest that the pandemic will remain during most of 2021 and even 2022 [8]. The current treatment is limited to symptomatology and standard therapeutics for viral pneumonia, mainly consisting of supportive care measures like oxygenation through nasal cannula, noninvasive airway or mechanical ventilation, hydration either via supervised oral intake or intravenous fluids, rest and filling of calories requirement [9]. China has been the first country declaring the control of COVID-19 outbreak in absence of a vaccine, testing several potential treatments, registering and communicating the clinical outcomes [10]. Hence, some antiviral treatments were preliminary recommended based on the Chinese, European and American experiences in the management of the disease. Nevertheless, the application of therapeutic alternatives is still limited to established institutional protocols based on scientific literature and the Colombian consensus on care, diagnosis and management of SARS-COV-2 / COVID-19 infection [11].

The latter is currently considered as outdated and guidelines published by the Instituto Nacional de Salud (INS) avoid explicit recommendations to supply drugs without sufficient scientific evidence, in line with the WHO guidelines. This contribution presents an overview of the current research on the major repurposed antivirals considered for COVID-19 and currently available or potentially available in Colombia.

2.Methodology

Previous studies in the field of infectious diseases have shown that bibliometric analysis constitutes a valuable tool for monitoring the research trends on a particular field as well as to identify their relevant characteristics [12–14]. For this study, data search and collection were performed in the Scopus database. The search strategy included the terms in the article title, abstract, and keywords. The "document type" was unconstrained, and software VOS viewer 1.6.10 was used for visualization and data analysis [15]. Additionally, trends of search interest on Google were obtained from Google Trends for specified terms related to COVID-19 in Colombia.

Scopus database

Search 1 (September 10, 2020): COVID-19 or 2019-ncov or SARS-CoV-2 and chloroquine and hydroxychloroquine. 767 documents.

Search 2 (September 10, 2020): COVID-19 or 2019-ncov or SARS-CoV-2 and lopinavir or ritonavir. 1,322 documents.

Search 3 (September 10, 2020): COVID-19 or 2019-ncov or SARS-CoV-2 and ribavirin or interferon or favipiravir or umifenivir or arbidol. 1,492 documents.

Search 4 (September 10, 2020): COVID-19 or 2019-ncov or SARS-CoV-2 and molecular docking and docking. 253 documents.

Search 5 (September 10, 2020): COVID-19 or 2019-ncov or SARS-CoV-2 and ivermectin. 106 documents.

Search 6 (September 10, 2020): COVID-19 or 2019-ncov or SARS-CoV-2 and remdesivir. 993 documents.

Google Trends

Search 7 (September 11, 2020): Chloroquine or Hydroxychloroquine

Search 8 (September 11, 2020): Ivermectin

Search 9 (September 11, 2020): COVID-19 test

3.Results and discussion

Evolution of research on COVID-19

From the first report on the novel coronavirus SARS-CoV-2 44,976 documents have been published, and 44,848 of them during 2020 because of the related COVID-19 pandemic.

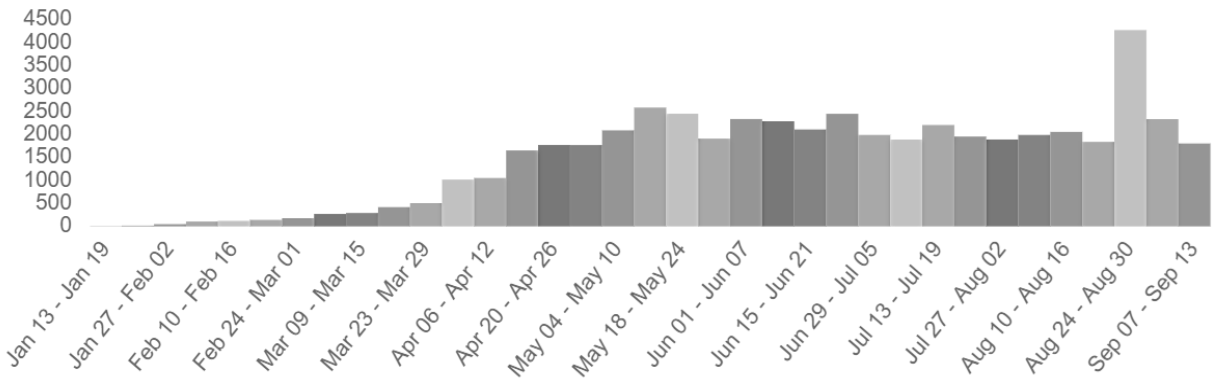
The evolution of weekly published papers is presented in Figure 1a. The number of publications increased substantially after the pandemic declaration by the WHO in March 2020. From May 11, 2020 onwards the number of publications on the field is rather stable with a mean of 2,160 publications per week in the last 17 weeks, with a maximum of 4,267 publications (August 26-30, 2020) and a minimum of 1,889 publications (July 06-12, 2020). The increasing research on SARS-CoV-2 comprises transmission and drug mechanisms (5,535 publications), human-human transmission (1,526 publications), diagnosis (7,943 publications), treatment (11,743 publications), prevention (18,649 publications), case reports (3,395 publications), forecasting and modelling (797 publications). As expected, and presented in Figure 1b, most of the publications belongs to medicine area (53.1%), followed by biochemistry (7.3%) and social sciences (5.8%).

COVID-19 in Colombia

The high number of cases in Italy, Spain and the U.S presented on March, 2020 inevitably led to the arrival of the SARS-CoV-2 to Colombia, since those destinations are among the most frequented by the Colombian citizens [(17)]. During the first days of the disease in the country the number of infections grew at a mean rate of twenty cases per day and considering the early poor detection and testing capacity, it was a significant number. In such early stages 62.7% of the total contagions were imported from foreign countries, namely Spain (38%), U.S (9.7%), Italy and E.U countries (15%). Moreover, before the confirmation of the arrival of the disease, 640,558 people entered to the country through the international airports during January and February 2020 and 50% of them arrived from the critical COVID-19 hotspots, namely Spain (10%), U.S (33%), E.U countries (3.5%) and only 0.6% from Asia (0.03% from China) and most of them (60%) entered through Bogotá D.C [(18)].

Colombia has been on the top-ten of total new cases as well as total and new deaths caused by COVID-19 although the growth trend seem to be decreasing. Nevertheless, the number of tests per million inhabitants is still very low, under-recording of cases and uncertainties about the real circulation of the virus are plausible. Under the lockdown measures taken by the authorities during several months in 2020, the sales of the over-the-counter drugs increased up to 82% and the interest on drugs promoted as treatments against COVID-19 were in the top of internet searchs in the country [(19)]. Initially,

(a)



(b)

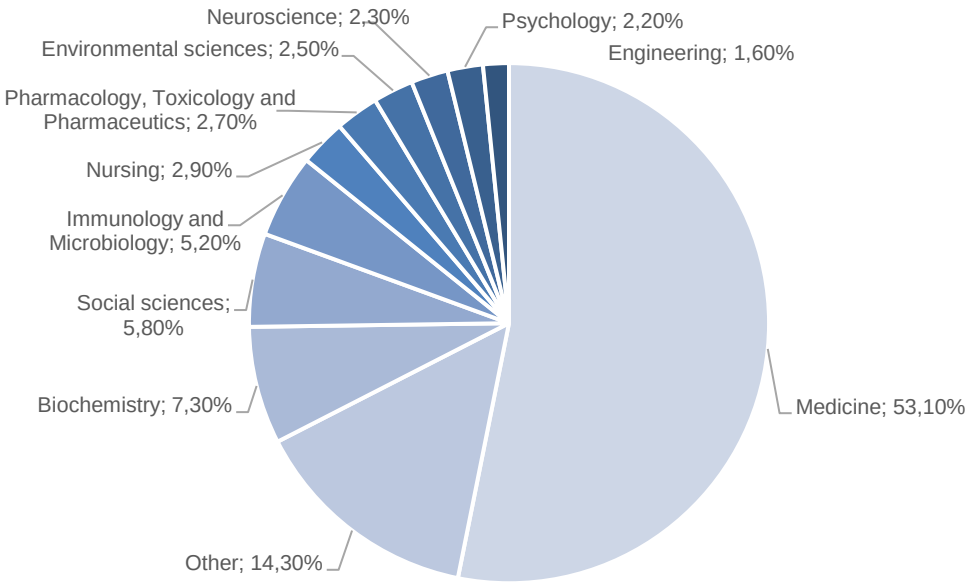


Figure 1. *Contributions of COVID-19/2019-ncov/SARS-CoV-2.* ***(a)*** *Evolution of weekly published papers (adapted from Chen et al)* [16]*.* ***(b)*** *Percentage of contributions per area of knowledge.*

antimalarial chloroquine and hydroxychloroquine attracted attention. More recently the antiparasitic ivermectin did it, as observed in Figure 2a.

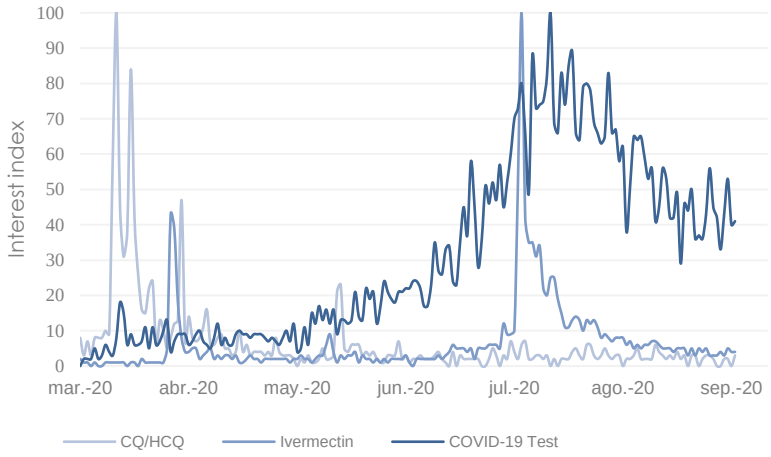
The accumulative trend of cases, as well as the search-trend of COVID-19 tests and antiparasitic ivermectin in Google (Figure 2a) suggest that a significant number of people suspected of being infected with the coronavirus and might self-medicate with this substance. Interestingly, this coincides with the officially-registered epidemiological peak of the pandemic (Figure 2b). Thus, the high circulation of the virus and self-medication might have played an important role in the epidemiological trends currently observed in the country.

Antimalarials chloroquine and hydroxychloroquine

The need for effective antiviral treatments to face the COVID-19 placed some repurposed drug compounds in the view of the scientific community as available alternatives in the short term for the clinical management of the disease. Among those compounds, the antimalarial Chloroquine (CQ) and its hydroxylated analog Hydroxychloroquine (HCQ) were in the spotlight in the early stages of the pandemic due to their potential antiviral effect, low cost and readily high availability [2,20]. CQ has been considered the most successful and studied antimalarial drug owing to its cost, availability, and antiparasitic efficacy (21). However, the prophylactic and therapeutic use of CQ/HCQ in malaria has decreased because of the antimicrobial resistance phenomenon. CQ and HCQ have gained importance in the treatment of other diseases [21] and both, the U.S Federal Drug Administration (FDA) and Chinese Center for Disease Control (China CDC) authorized the use of these drugs in COVID-19 patients [22].

CQ/HCQ act as weak bases due to the secondary and tertiary amine groups. The intracellular pH increase of lysosomal and trans-Golgi network vesicles disrupts the enzymatic function and inhibits the post.

(a)



(b)

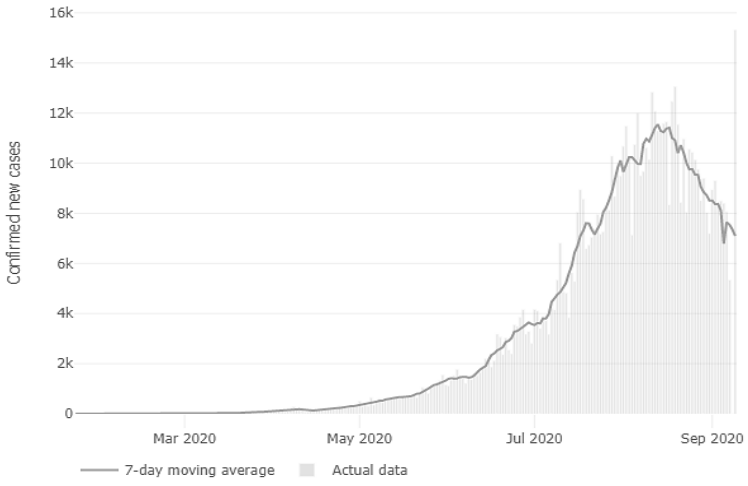


Figure 2. *Trends related to COVID-19 in Colombia.* ***(a)*** *Search-trend of COVID-19 tests and antiparasitic ivermectin in Google.* ***(b)*** *Accumulative trend of cases in Colombia (adapted from Coronavirus Resource Center, Johns Hopkins University & Medicine).*

translational modification of the synthesized proteins [23,24]. Thus, the antiviral effect depends on the virus use of endosomes to infect the host-cells [25]. CQ/HCQ can also diminish the surface expression of the glycosylated forms of ACE2 receptor affecting negatively the binding between ACE2 and S glycoproteins of coronavirus [25]. The first report referring the potential antiviral effect of CQ demonstrated that viral titers may decrease when treated with CQ before and during virus inoculation, but it was ineffective if applied 8-12 hours post inoculation [24]. Based on those results, Savarino et al (2003) hypothesized that CQ/HCQ might help in the management of SARS-CoV by affecting the endosomal transport [23]. Moreover, those results suggest that efficacy of the drug decreases depending of the extent of the infection on the cells, possibly explaining the poor clinical outcomes when applied in late phases of the COVID-19.

CQ has been reported as an effective *in vitro* inhibitor of SARS-CoV-2 in Vero E6 cells (EC90 of 6.90 μM) [26]. In addition to its antiviral activity, CQ/HCQ has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*. *In vitro* tests with HCQ in Vero cells also showed inhibition of SARS-CoV-2 infection (EC50 of 0.72 μM) (27). Another study reported that CQ could inhibit the SARS-CoV 2 in Vero E6 cells at EC50 of 7.36 μM while HCQ did it at EC50 of 12.96 μM (28). Based on physiologically-based pharmacokinetic models a loading dose of 800 mg of HCQ followed by a maintenance daily dose of 400 mg for 4 days was recommended for treating the SARS-CoV-2 infection [27]. The latter is equivalent to three times the effect of chloroquine at daily doses of 1000 mg during 5 days [27]. As prophylactic measure, CQ has been recommended based on the established pharmacokinetics for treatment of malaria and autoimmune diseases. It has been referred that a safe and potentially efficacious dose for protection against SARS-CoV-2 would be in the order of 250-500 mg daily and a post-exposure dose of 8 mg/kg/day for 3 days [29]. However,

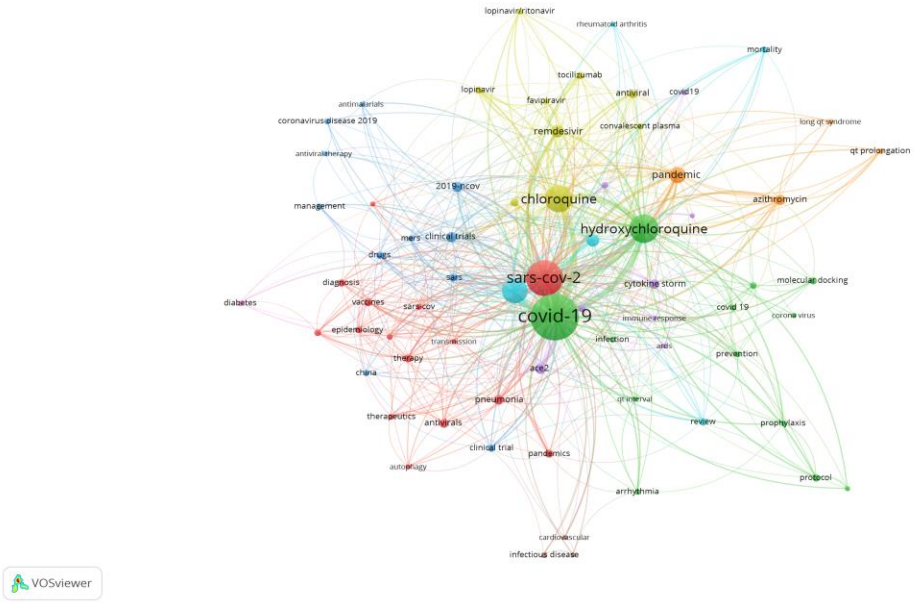


Figure 3. *Bibliometric network of studies related to COVID-19/2019-ncov/SARS-CoV-2 and CQ/HCQ. Note: the minimum number of occurrences of a keyword is 5.*

there is no clinical evidence about the effectivity of such prophylactic doses for preventing infection with SARS-CoV-2. 767 scientific reports relating COVID-19/2019-ncov/SARS-CoV-2 and CQ/HCQ were identified, and its bibliometric network is showed in Figure 3, which contains 69 nodes within 9 clusters.

The effectivity and risks associated to the use of the drug for treating the SARS-CoV-2 infection is still controversial. In Colombia the use of CQ/HCQ was initially suggested for patients non-associated with the drug contraindications and only in the cases of severe pneumonia, acute respiratory distress syndrome, sepsis and septic shock (11). Such scheme considered a dose of 400 mg HCQ every 12 hours on day 1, followed by 200 mg every 12 hours for the next 5 days; in case of CQ, 300 mg every 12 hours for 10 days [(11)]. Some reports remarked the effects on cardiac conduction, with a prolongation of the QT interval and increased risk of ventricular arrhythmias in patients presenting cardiopulmonary compromise associated with the virus pathophysiology [(11)].

On April, 2020, an increase of demand for CQ/HCQ occurred due to widespread publicity of small and uncontrolled trial performed in France on March, 2020 [(22)]. This study suggested that the combination of HCQ with the macrolide azithromycin was successful in clearing viral replication [(20)]. Then, several countries have been stockpiling the drugs, and shortages occurred [(22)]. Currently, the prices of CQ/HCQ increased more than 100%, affecting the access to this drug required for treatment of malaria and some auto-immune diseases. In this regard, Colombia has a high circulation rate of the malaria vector owing to its geographical location and climatic conditions.

As consequence of stockpiling and price rise, low inventories of CQ/HCQ might have implications for the endemic malaria regions since both drugs constitute the current first-line

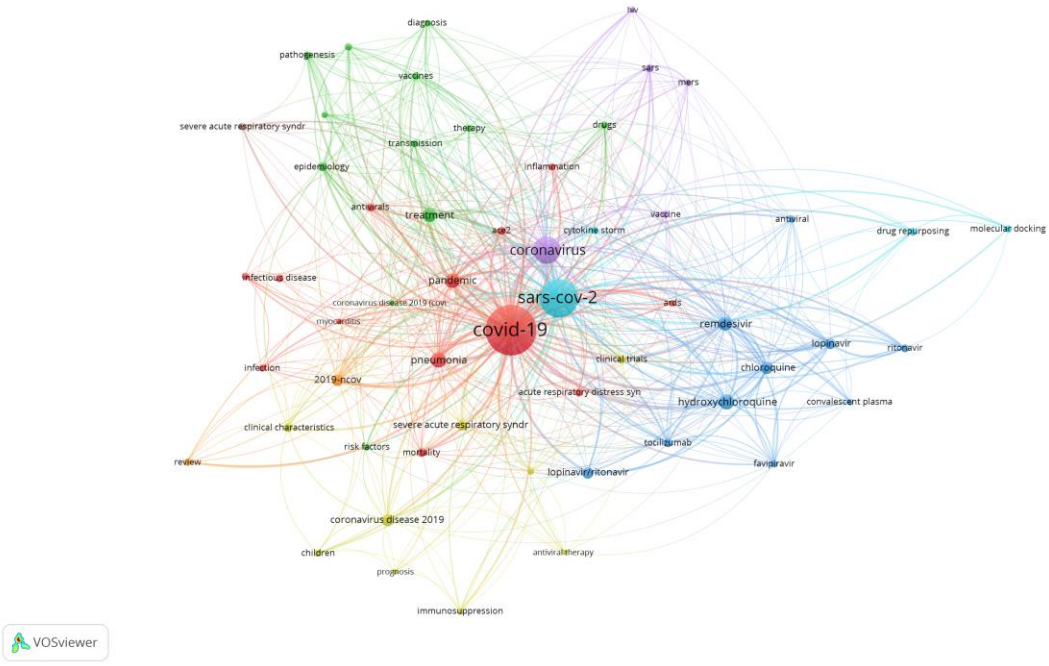


Figure 4. *Bibliometric network of studies related to COVID-19/2019-ncov/SARS-CoV-2 and LPV/r. Note: the minimum number of occurrences of a keyword is 10.*

treatment for malaria by *Plasmodium vivax*. Furthermore, CQ/HCQ is widely used in systemic lupus erythematosus and rheumatoid arthritis due to its anti-inflammatory and modulating effect. According to the national food and drug authority (INVIMA), there are only 5 licensed local manufacturers, in addition to 1 from India and 1 from Spain, which also explain the fall in supplies after the quarantine declaration.

HIV-1 protease inhibitor Lopinavir/Ritonavir

Lopinavir/ritonavir (LPV/r) is a pharmaceutical combination known by its commercial name Kaletra®. This formulation inhibits HIV-1 proteases triggering an antiviral effect in both, on virions maturation and cellular infection [30]. The viral proteases are endopeptidase enzymes that catalyze the cleavage of peptide bonds of viral polyproteins and host-cells proteins, which are necessary for viral maturation, life cycle and further infection [31]. LPV/r combination has been tested in treatment of coronavirus infection with MERS-CoV. Initial *In vitro* tests with LPV in Vero cells for MERS-CoV showed suboptimal EC50 in the inhibition assay [32]. Application of post-exposure prophylaxis with LPV/r decreased the infection risk (40%) in healthcare workers [33].

Currently, a recursive two-stage group sequential randomized controlled trial for the treatment of MERS-CoV with a combination of LPV/r and interferon-β1b (MIRACLE trial) is currently under development in Saudi Arabia [34,35]. Based on the previous tests with MERS-CoV, LPV/r has been explored experimentally in COVID-19 individual cases and clinical trials, but the outcomes also remain controversial. 1,322 studies have been published on LPV/r and SARS-CoV-2 and its bibliometric network is shown in Figure 4, which contains 56 nodes within 8 clusters.

The use of LPV/r was recommended in some

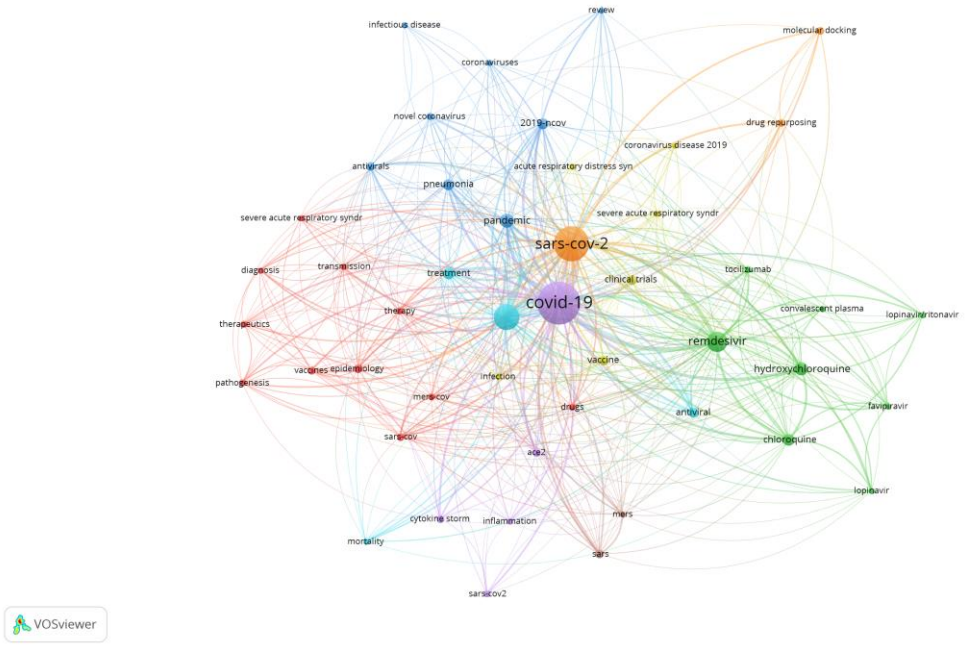


Figure 5. *Bibliometric network of studies related to COVID-19/2019-ncov/SARS-CoV-2 and remdesivir. Note: the minimum number of occurrences of a keyword is 10.*

COVID-19 treatment protocols in the early stages of the pandemic in Asia [36–38]. Information on retrospective studies showed have shown conflicting results. For instance, retrospective studies in China showed a reduction of 6 days in median duration of viral load in patients treated with LPV/r (65%) in comparison with the untreated group (35%) (39). However, early administration (≤10 days from symptom onset) led to better outcomes. This coincided with the poor clinical outcomes observed in severe patients treated with LPV/r combination [40]. In contrast, another retrospective study in China showed no significant difference between the LPV/r treated and untreated groups [41].

LPV/r is readily available in Colombia and it is currently used as part of the treatment scheme for VIH patients. Fortunately, shortages of LPV/r were not evidenced in the country, possibly due to lower diffusion of the positive results of this drug on COVID-19 patients, in addition to the higher selling price of the formulation. The Colombian consensus recommended an scheme with LPV/r (400/100 mg every 12 hours during 7-14 days), even in combination with CQ/HCQ in the cases of severe pneumonia, acute respiratory distress syndrome, sepsis and septic shock [11].

Currently, the interest on CQ/HCQ and LPV/r as treatment for COVID-19 has decreased due to lack of effectivity on severe patients and hence, its use is already practically ruled out in the clinical practice.

Adenosine analog Remdesivir

Remdesivir (GS-5734) is a novel antiviral adenosine analog, developed as treatment for Ebola virus. Remdesivir is a nucleotide analog inhibitor of RNA-dependent RNA polymerases (RdRps) with antiviral activity against several single stranded RNA viruses [42,43].

This compound has been previously tested in both, SARS-CoV and MERS-CoV, showing effective inhibition. *In vitro* (Calu-3) and *in vivo* assays in animal models showed effectivity in reducing the viral load and improving the respiratory function, decreasing the severity of disease and lungs damage when administered either pre or post-infection, suggesting that remdesivir could be a potential treatment also for SARS-CoV-2 even more than LPV/r based treatments [44,45]. Remdesivir showed effectivity against SARS-CoV-2 post-infection *in vitro* using Vero E6 and Huh-7 cells (EC90 of 1.76 μM) [26]. 993 studies have been published on Remdesivir and COVID-19/2019-ncov/SARS-CoV-2, showing a bibliometric network of 47 nodes and 8 clusters (Figure 5).

Results of clinical trials in COVID-19 patients with lower respiratory tract involvement look promising. Patients have been treated with 200 mg loading dose on day 1, followed by 100 mg daily for up to 9 days. Results indicated that remdesivir was superior to placebo in a median shortening the time to recovery of 4 days (15 vs 11 days) [46]. Currently, Remdesivir is the only drug authorized to treat COVID-19 in the United States, although the approval was made following an emergency procedure and the drug has not yet received final approval from the FDA. According to the manufacturer, enough doses of this intravenous drug to satisfy global demand is guaranteed and Colombia is participating on the clinical trials with Remdesivir since August, 2020. Remdesivir is not commercially available in Colombia and the high cost per patient (3000 USD), limit its potential application in the short term in the country.

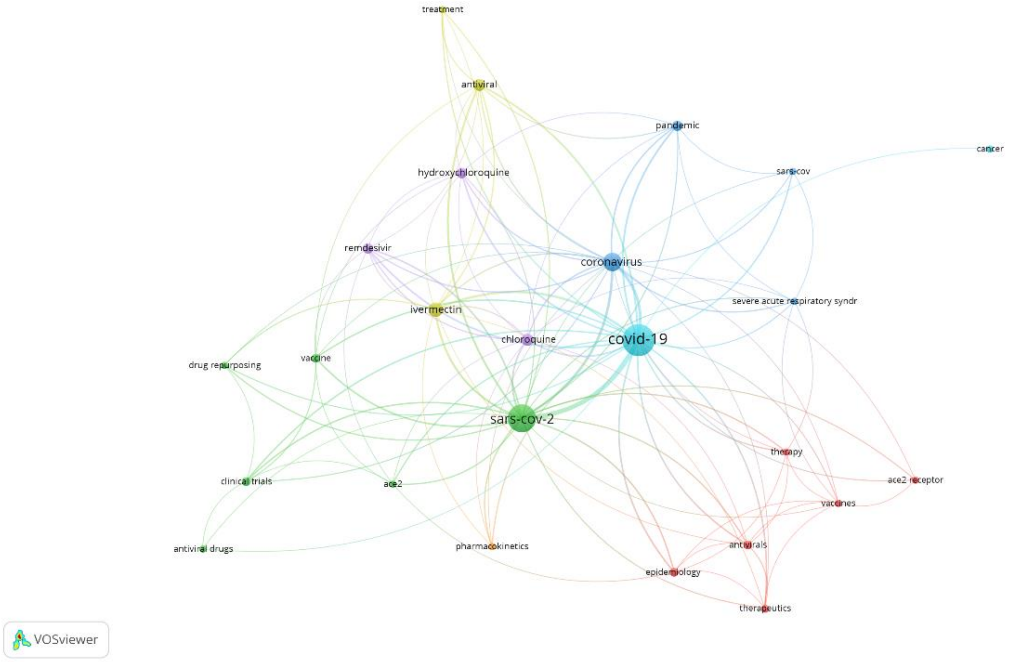


Figure 6. *Bibliometric network of studies related to COVID-19/2019-ncov/SARS-CoV-2 and Ivermectin. Note: the minimum number of occurrences of a keyword is 3.*

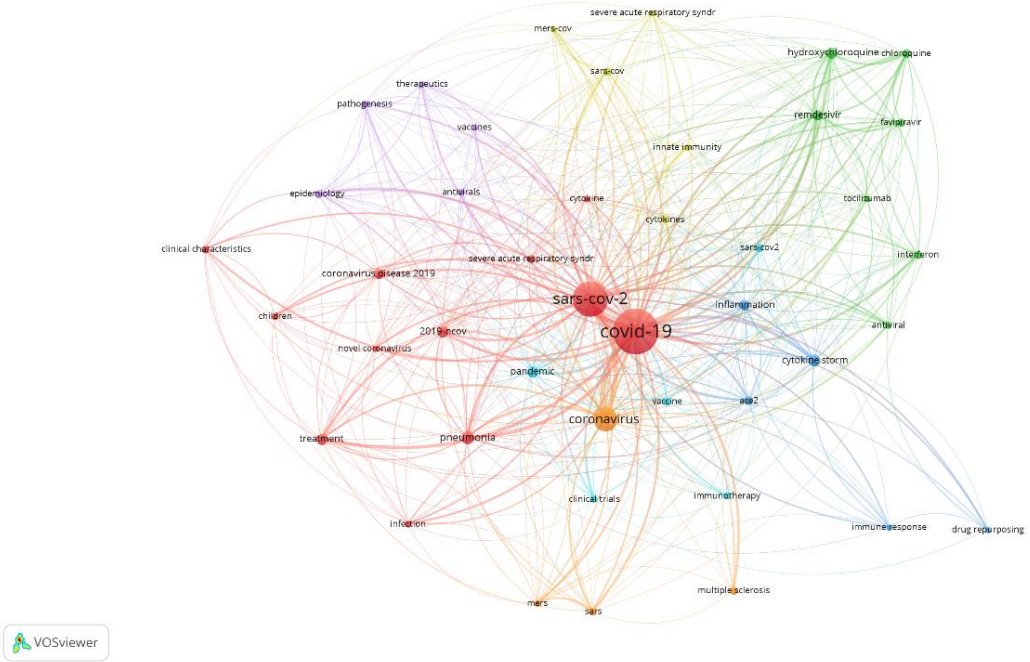


Figure 7. *Bibliometric network of studies related to COVID-19/2019-ncov/SARS-CoV-2 and ribavirin or interferon or remdesivir or favipiravir or umifenivir or Abidol. Note: the minimum number of occurrences of a keyword is 15.*

Antiparasitic Ivermectin

Ivermectin is a semisynthetic broad-spectrum anti-parasitic that targets GABA-mediated neurotransmission and binds glutamate-gated chloride channels in invertebrates and globally used in the clinical practice in humans and animals [47,48]. Ivermectin exhibits also activity against several RNA viruses such as dengue, influenza, RSV, and rabies [48].

Caly et al. (2020) reported a 5,000-fold reduction in SARS-CoV-2 RNA levels, compared with the control. Infected Vero/hSLAM cells were incubated for 48 hours with 5 μM ivermectin. The ivermectin IC_{50} for the virus was calculated at approximately 2.5 μM, which are equivalent to 4,370 and 2,190 ng/mL, respectively. Pharmacokinetic studies have suggested that single doses up to 120 mg of ivermectin can be safe and well tolerated, although such dose is 10-fold greater than those approved by the US Food and Drug Administration, the C_{max} reported in vitro was 250 ng/mL, which is lower than the effective in vitro concentrations against SARS-CoV-2 [47]. Simulations with pharmacokinetic models to predict total plasma concentration-time profiles of the approved dose of ivermectin (200 μg/kg) have shown that plasma ivermectin concentrations do not reach the *in vitro* IC_{50} required for SARS-CoV-2 [49]. The bibliometric map (Figure 6) shows 25 nodes, 7 clusters and 106 documents evidencing the increased attention that ivermectin is attracting as repurposed drug for COVID-19 treatment. At high doses, the drug could penetrate the blood-brain barrier and affect GABA-gated transmission in patients with increased endothelial permeability in hyperinflammatory stages [47,48]. Thus, human overdose has been associated with several adverse effects, including depression, ataxia, psychosis, confusion, and seizure [48].Nevertheless, an *in vivo* effect may be possible even if efficacious in vitro concentrations are physiologically unattainable [47]. Further studies in vivo and in the clinical level must be carried out to confirm the referred inhibitory effects on the replication of SARS-CoV-2 at safe doses of the drug.

Other antivirals tested for COVID-19 treatments

Few studies have been published involving different antivirals with reduced availability or less proven benefits in COVID-19 treatment; among them, the Type I interferons α and β, ribavirin, remdesivir, favipiravir and umifenivir (Abidol) are the most studied. In this regard, 1,492 studies have been published and its bibliometric network is showed in Figure 7. In Figure 7, 43 nodes and 7 clusters are observed.

On virus detection, Type I interferons (IFNs) are secreted by infected cells having a plethora of functions, including the activation of antimicrobial programs in host cells and development immune responses [50]. Type I IFNs induce the transcription of IFN-stimulated genes (ISGs) in infected cells, which codify for proteins that suppress viruses by different mechanisms such as the inhibition of viral transcription, translation, replication, inducing nucleic acid degradation and altering membrane and lipid metabolism [51].

It has been demonstrated that IFN-α inhibits the coronavirus SARS-Co-V *in vitro* [52–54]. The review of clinical findings in patients with SARS-CoV in Guangzhou, China treated with four different protocols showed also that a treatment regime of IFN-α without corticosteroids led to need for mechanical ventilation in only 7% of the patients but high-dose corticosteroids concomitant with IFN-α avoided the need for mechanical ventilation in the 100% of patients [55]. In the case of SARS-CoV, the antiviral ribavirin used for treatment of respiratory syncytial virus in combination with interferon α for chronic hepatitis C was also

initially tested *in vitro*, but results were not conclusive [53,54]. However, a synergistic effect was observed between Type I IFNs and the antiviral Ribavirin in both coronaviruses SARS-CoV and MERS-CoV [53,56–58]. An important limitation of ribavirin is its significant toxicity at the high doses required for treatment in SARS-CoV patients, but the sensitivity of MERS-CoV is 50–100 times higher for the interferon-ribavirin than SARS-CoV [59,60].

Previous findings related to the effects of interferons with corticosteroids or ribavirin on coronavirus diseases suggested that those combinations might be potential treatments for pneumonia associated to the SARS-CoV-2 infection. Lokugamage et al. (2020) found that pretreatment of SARS-CoV-2 with INF-α reduce viral replication at 24 and 48 hours post infection in Vero E6 cells compared to control and SARS-CoV [61]. This is consistent with the recommendations of the Chinese Disease Control Centre and the expert consensus for COVID-19 treatment in children (10,62). Moreover, the treatment of critical care and non-critical care patients with INF-α combined with methylprednisolone, moxifloxacin and LPV showed preliminary positive results in 74% of CCU patients, allowing them to be transferred out from the CCU and most of the non-CCU patients improved with only mild symptoms [63].

However, treatments involving Type I INFs combined either with corticosteroids or antivirals requires further studies. In this regard, 59 clinical trials are registered in the U.S National Institutes of Health (NIH) as using INFs as treatment alternative for COVID-19 [64]. Currently, the application of Type I INFs and ribavirin are not recommended in Colombia due to higher toxicity risks without conclusive potential benefits in COVID-19 treatment [11]. Additionally, there is no consensus about the use of corticosteroids, alone or in combinations, in COVID-19 patients.

Another nucleoside analog is the Favipiravir (T-705, Avigan, Favilavir), developed and licensed as an anti-influenza drug in Japan. Favipiravir is stockpiled for 2 million people as a countermeasure for novel influenza strains [65]. Recently, Russia has claimed a Favipiravir analog (Afivavir) as the first successful drug for treating COVID-19 after approval by the Russian Ministry of Health [66]. This group of drugs have also an inhibitory effect on the RdRp. Favipiravir has previously shown efficacy *in vitro* and *in vivo* against other RNA viruses including Ebola virus, Lassa virus, rabies, and severe fever with thrombocytopenia syndrome with apparent lack of generation of resistance phenomena [65]. *In vitro* tests using Vero E6 cells indicated that high doses of favipiravir are required to have inhibitory effects on SARS-CoV-2 reduce the 2019-nCoV infection in ($EC50 = 61.88\ \mu M$, $CC50 > 400\ \mu M$) [67].

A clinical trial considering a loading dose of 1600 mg twice followed by 600 mg twice daily from between days 2 and 14, showed that shorter viral shedding time occurred in the treated patients with (2.5–9 days) in comparison with the untreated group (8–13 days). Also, significant improvement was observed in chest imaging compared with the control, with an improvement rate of 91.43% versus 62.22%. Currently, there are 22 clinical trials registered in the NIH relating favipiravir and COVID-19 (64). This drug is not available in Colombia, therefore is not recommended for COVID-19 treatment in the country so far.

Umifenovir (Arbidol®) is considered a broad-spectrum antiviral with activity against influenza A and B, hepatitis B and C, and even against SARS virus. It has been recommended by the China CDC for COVID-19 treatment with dosing of 200 mg, three times a day during maximum 10 days. In vitro it has been reported that Arbidol can effectively inhibit the SARS-CoV infection at the concentration of 10-30 μM

in vitro affecting the fusion process [68]. A study compared the antiviral effects of LPV/r and Arbidol in patients infected with SARS-CoV-2 and treated according to the Chinese guidelines.

No differences were observed in fever duration between the two groups and no viral load was detected in arbidol group after 14 days while the patients treated with LPV/r remained with viral load, indicating that Arbidol monotherapy was superior to LPV/r treatment. Similarly, a prospective, randomized, controlled, open-label multicenter trial involving COVID-19 patients were treated with Arbidol (200 mg three times a day) or Favipiravir (1600 mg twice a day, followed by 600 mg twice a day) for 10 days but clinical recovery rate at day 7 did not differ significantly in both groups and favipiravir improved the latency to relief fever and cough. Only 8 clinical trials are registered in the NIH relating umifenovir (Arbidol) and COVID-19 [64]. As the case of remdesivir and favipiravir, this drug is also not available in Colombia and hence, it cannot be recommended as treatment option for COVID-19 patients in the country.

Perspectives of new antivirals for mitigating COVID-19 based on computational studies

International emergence of COVID-19 is motivating research groups around the world to understand the molecular basis of SARS-CoV-2 and to propose new possible drug-targets and treatments by means of systems biology and bioinformatics approaches. Molecular Docking is a powerful method for identifying *in silico* drug-targets candidates by means of prediction of protein-ligand bounds and the computation of free energies of binding between ligand and protein targets [69]. The method allows to make virtual screenings of ligand libraries containing thousands of compounds in a faster way, and generate a list of possible drug targets that can be tested experimentally (70). Recently, a moderate number of researches has focused their efforts in the virtual screening of compounds for treating SARS-CoV-2 [71–73]. Figure 8 shows a bibliometric network of studies related to

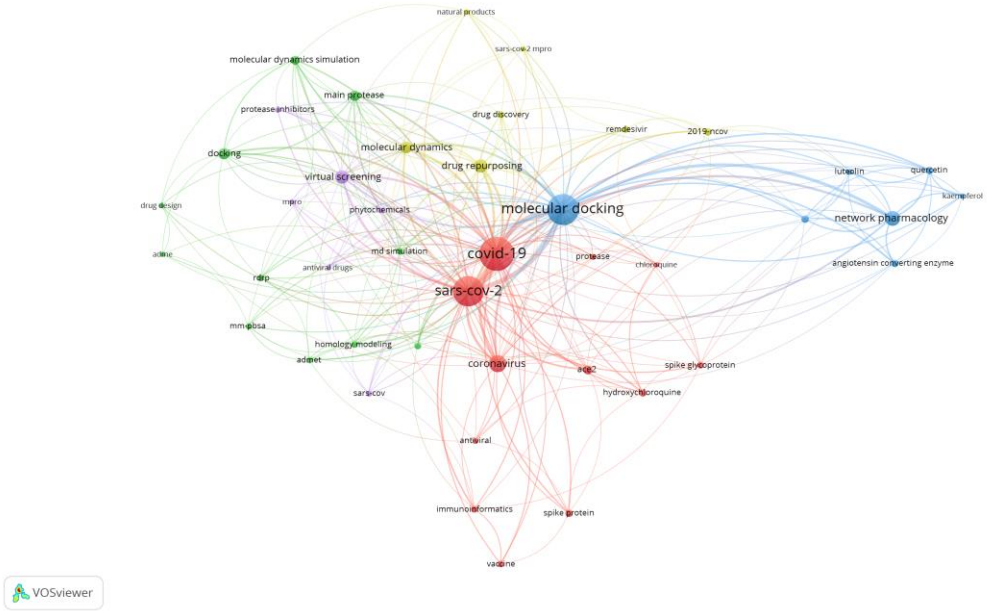


***Figure 8**. Bibliometric network of studies related to COVID-19/2019-ncov/SARS-CoV-2 and molecular docking/docking. Note: the minimum number of occurrences of a keyword is 5.*

COVID-19/2019-ncov/SARS-CoV-2 and molecular docking (43 nodes within 5 clusters).

Recent docking studies have been mainly focused on RdRp enzyme [71,73]. Lung and colleagues develop a molecular docking for studying the interaction ligand-protein between RdRp from SARS-CoV-2, SARS-CoV and MERS-CoV and a database of chemical structures from the traditional Chinese medical compounds [71]. The main result of this study was the identification of theaflavin as a best inhibitor (lower binding energy) that targets RdRp. Theaflavin is a polyphenol of black tea with known functions as antioxidant and inhibitor of pathogenic organisms [74]. Similarly, Elfiky (2020) studied the interaction between polymerase inhibitors and RdRp, and demonstrated that sofosbuvir, ribavirin, and remdesivir could be drug candidates against RdRp of SARS-CoV-2 [73].

Robson et al (2020) applied bioinformatics, structural biology simulations and docking for proposing synthetic vaccine epitopes [75]. Choudhary and colleagues (2020), focused their efforts in drugs for blocking the interaction between S glycoprotein and the ACE2 host cell receptor [76]. They made a high-throughput screening of the FDA approved LOPAC (Library of Pharmacologically Active Compounds) drugs with interesting results. Drugs like GNF5, TNP, GR and Eptifibatide shown to be candidates for inhibiting S glycoprotein and ACE2 interaction, with GNF5, TNP known by inhibitory effects on MERS-CoV infections [77,78]. Smith and colleagues 2020 also studied through docking the possible drugs that can inhibit the interaction between ACE2 and S glycoprotein [79]. Some of them (pemirolast, benserazide, and isoniazid pyruvate) are under regulatory review in the United States.

Other researchers have been interested in finding drug candidates for inhibition of virus proteases [80,81]. Ton and colleagues (2020) developed a deep learning approach named Deep Docking that allows to make virtual screening of billions of compounds that can interact with SARS-CoV-2 main protease (Mpro). A list of 1000 chemically diverse candidates were found, with LPV (the clinically approved HIV protease inhibitor) and other pre-clinical drugs as best inhibitor candidates. Tahir ul Qamar and colleagues, 2020, decided to analyze the ligand-protein interactions with the viral 3-chymotrypsin cysteine protease enzyme, which controls coronavirus replication and life cycle [81]. They tested 32,297 potential anti-viral phytochemicals and found that Licoleafol, Amaranthin, Myricitrin, Colistin, Nelfinavir among others may inhibit SARS-CoV-2.

Interestingly, LPV/r, ribavirin, remdesivir and CQ/HCQ , currently being tested clinically as promising therapies for SARS-CoV-2 infection, have been also resulted in the computational screening of drug compounds for treating the COVID-19 [82–84]. Although most of the other candidates need to be tested experimentally *in vitro* and *in vivo*, docking is a great tool for generating fast hypothesis and helping researchers to reducing time and experimental spectrum of testing drugs during the actual emergence.

4. Conclusions

In Colombia, chloroquine/hydroxychloroquine, lopinavir/ritonavir and ivermectin are the only marketed repurposed antivirals available as potential treatments of COVID-19 patients in absence of vaccine and other validated therapeutics while Remdesivir is currently part of a testing program. The evidence related to their effectivity and safety remain still controversial especially in hospitalized and severe patients. With exception of Remdesivir,

most of the scientific efforts are focused in the vaccine development and production. Repurposed over-the-counter drugs like chloroquine, hydroxychloroquine, lopinavir/ritonavir and ivermectin are cheap enough to be accessible for all people but the current discussion about their effectiveness make difficult their application in the clinical or ambulatory treatment of COVID-19. However the possible benefits of these medications are more likely in patients with a mild course of the disease than in severely ill patients. Also the impact of self-medication of people with those over-the-counter drugs in the evolution of the pandemic in the country remains to be assessed. Computational strategies are promising tools to identify new and more effective compounds for the current and future pandemics, but government, academy and industry should cooperate to accelerate the developments and anticipate crisis like the one we are currently facing with the COVID-19, while clinical protocols must be adapted to rapidly respond the development and assessment of licensed and new antivirals

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