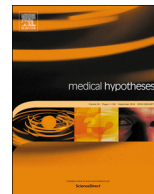**ELSEVIER**

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Serum albumin-mediated strategy for the effective targeting of SARS-CoV-2

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ABSTRACT

Novel coronavirus (NCoV-19), also known as SARS CoV-2, is a pathogen causing an emerging infection that rapidly increases in incidence and geographic range, is associated with the ever-increasing morbidity and mortality rates, and shows sever economic impact worldwide. The WHO declares the NCoV-19 infection disease (COVID-19) a Public Health Emergency of International Concern on 30 January 2020 and subsequently, on March 11, 2020, declared it a Global Pandemic. Although some people infected with SARS CoV-2 have no symptoms, the spectrum of symptomatic infection ranges from mild to critical, with most COVID-19 infections being not severe. The common mild symptoms include body aches, dry cough, fatigue, low-grade fever, nasal congestion, and sore throat. More severe COVID-19 symptoms are typical of pneumonia, and upon progression, the patient's condition can worsen with severe respiratory and cardiac problems. Currently, there is no drug or vaccine for curing patients. It has been observed that people with challenged immunity are highly prone to SARS CoV-2 infection and least likely to recover. Also, older adults and people of any age with serious underlying medical conditions might be at higher risk for severe forms of COVID-19. We are suggesting here a strategy for the COVID-19 treatment that could be effective in curing the patients in the current scenario when no efficient medicine or Vaccine is currently available, and Clinicians solely depend upon the performing trials with drugs with known antiviral activities. Our proposed strategy is based on the compilation of published scientific research and concepts. The different published research indicates the success of a similar strategy in different physiological conditions, and such a strategy is widely studied at the cellular level and in animal models.

Important information on finding a strategy for the COVID-19 cure

NCoV-19 or SARS CoV-2 first emerges in the Wuhan city of Hubei province of China in December 2019, and since then, this virus is rapidly spreading to the different parts of the world and causing the fatalities at a devastating rate particularly in the Italy, Spain, and United State [1,2]. The virus is given name Coronavirus due to the similarity of its spike protein to the crown (*Latin* corona) [3]. SARS CoV-2 virus belongs to group IV Coronaviruses and is the member of the order Nidovirales, Family Coronaviridae, Subfamily Coronavirinae, and Genus Betacoronavirus [4]. The virus genome is a ~30 kb positive-sense single-stranded RNA that encodes structural, non-structural and accessory proteins. The virion is enveloped and spherical with a diameter of 60–140 nm and with the spike length of 9–12 nm. The phylogenetic study suggested a closer relation of this virus to bat-SL-CoVZXC21 and bat-CoVZC45 than to human SARS [5]. The early cases reported infection in people after attending the seafood and animal market, thereby suggesting the animal to human transmission of the virus. The later cases indicated the sustained human to human transmission of SARS CoV-2 [6,7]. Human to human transmission occurs through respiratory droplets and fomites. The primary site of infection is in epithelial cells of respiratory or enteric tracts while secondary sites are kidney and heart though in question [8]. Currently, there is no cure for the COVID-19, and clinicians are solely depending upon the drugs that could provide symptomatic relief. The clinical trials are performed using drugs that have been known to treat other viral infections/related diseases.

Our purpose in writing this hypothesis article is to shed some light on the well-known facts and highlight the strategy that can be used for COVID-19 treatment. The drugs or therapeutic materials are likely to be

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effective in the COVID-19 treatment if they either block the entry of the viral particles to cells or block the intracellular viral components [9]. The latter property plays one of the important roles in halting the propagation of viruses from infected cells while blocking the virus particles at the extracellular site inhibits the cell infection. Many factors define the effectiveness of the drug molecules, including their sustainability in the environment and cell penetration capacity.

To efficiently treat the SARS-CoV-2 infection, we are proposing the strategy of simultaneous targeting the viral particle extracellularly and intracellularly. To ensure the effective internalization of the potential drugs with demonstrated activity against the viral protease, polymerase, and RNA, serum albumin could be used as an excellent delivery vehicle. Serum albumin is a multifunctional protein known to interact with a range of exogenous and endogenous compounds. It is predominately present in the extracellular space, with high concentration being reported in the skin, guts, muscles, fluids (cerebrospinal, pleural), and secretions such as sweat, tear, milk, and saliva [10]. The well-known fact about albumin is that there is a complex relationship between the inflammation and albumin level in the extracellular matrix under various physiological and pathological conditions [11–13]. The earlier studies indicated that the stressed and inflamed cells increase the uptake of albumin [11–13].

We are suggesting the use of combinatorial drugs therapy, in which one drug inhibits the fusion and entry of the virus into the cells and another drug internalizes and targets multiple viral components inside the cell and/or cell signaling to halt the viral propagation (see Fig. 1).

Table 1 shows the list of drugs that have been shown to improve the state of the SARS-CoV-2 infected patients [8,14]. The drug combination has been chosen in such a way that it can effectively neutralize both extracellular and intracellular viral components. Furthermore, the serum albumin should be used to maximize the cellular internalization and enhance the pharmacological effects. A similar strategy based on the proposed concept was utilized in the influenza virus-infected mouse liver cells, where it yielded a positive outcome [15].

A recent search for the treatment of SARS-CoV-2 infection in PubMed revealed the usefulness of traditional medicine in treating the COVID-19 in the current pandemic [16]. For example, research indicated the high potential of the Epigallocatechin gallate (EGCG) and Curcumin in neutralizing the range of viruses [17–22].

The recent studies support the albumin therapy of COVID-19 patients since there is the complex relation of albumin concentration and ACE2 receptor expression in the cells, ACE2 receptors are crucial in mediating the virus infection [23]. If the albumin is used to stabilize and deliver the EGCG and Curcumin for targeting the intracellular virus components in combination with the drug that could block the virus fusion and/or entry to a cell, this strategy might represent an effective way of treating the SARS CoV-2 infection. EGCG and Curcumin combination is proven to be very effective in treating various pathological conditions by augmenting the key cellular signaling [24–26]. The inhibition of these key cellular pathways also helps in inhibiting the virus multiplication inside the cells as reported in the case of SARS-CoV [27–29]. In addition to their antiviral outcomes, curcumin and EGCG are known for their health-boosting properties [30,31].

Conclusion

In light of presented facts complemented by the referenced publications, it is highly recommended to use albumin as a therapeutic material, stabilizer, and deliverer of the drugs (such as known antiviral drugs and traditional molecules) that could effectively target the extracellular and intracellular viral components in the therapy of patients infected with SARS-CoV-2.

Competing interests

None declared.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
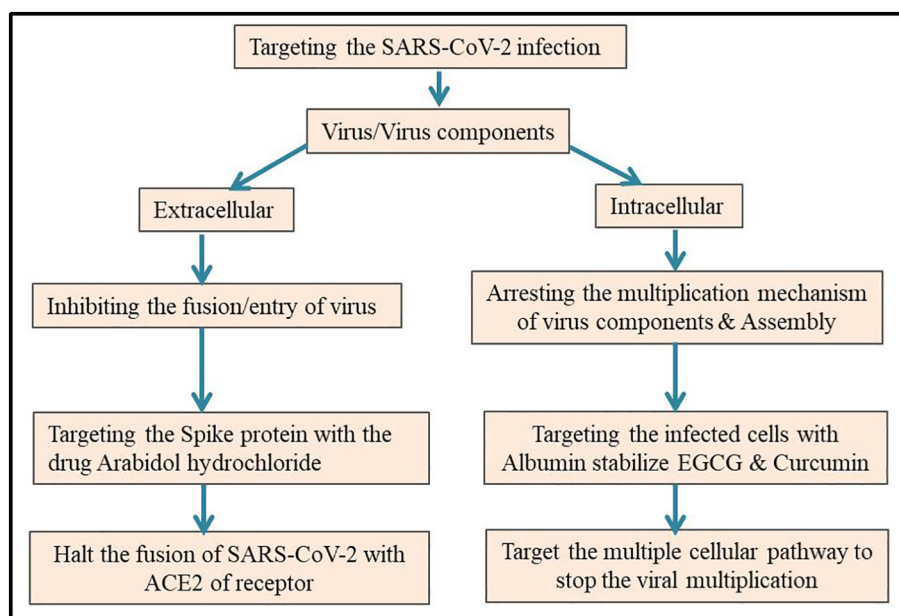
Fig. 1. Schematic representation of effective strategies for the treatment of SARS-CoV-2 infection.

Table 1
List of the drug molecules currently in use for treating the patients infected with SARS CoV-2.

S. No.	Drug	Description/Mechanism of action
1	Hydroxychloroquine	Decrease TLR signaling thus reduce activation of dendritic cells and inflammatory processes
2	Interferon alfacon-1	Induce the synthesis of key antiviral mediators and activate cytotoxic T cells
3	Lopinavir	Inhibit the activity of an enzyme critical for the HIV lifecycle
4	Remdesivir	Interfere with the activity of RNA polymerase thus could be effective in treating the variety of RN viruses.
5	Ritonavir	Protease inhibitor activity against HIV-1
6	Sofosbuvir	Inhibit the Hepatitis C NS5B protein thus used in the treatment of Hepatitis C infection
7	Umifenovir	Used in the prophylaxis and treatment of respiratory virus infection
8	Alfa-interferon	Broad-spectrum of Antiviral and Immune-regulatory activity with the subtypes acting synergistically to give a wide range of response
9	Corticosteroids	Class of steroid hormone use in the treatment of various physiological and pathological conditions
10	Ribavirin	Interfere in the RNA metabolism, such as blocking the viral RNA synthesis and mRNA capping require for viral replication

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109790.

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