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SARS CoV-2: Progression and treatment protocols – An overview

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ABSTRACT

COVID-19 pandemic is a global health crisis which has affected citizens of all nations. With more than a million death cases, this outbreak has already had a significant impact on the physical and mental well-being of mankind. Considerable amount of research is going on worldwide to find out effective drugs against the virus. Chloroquine phosphate, an antimalarial drug is currently used for the treatment. Studies on the harmful effects of chloroquine is in progress. India is rich in traditional medical practicing such as Ayurveda, Siddha, Unani etc. Ministry of AYUSH is trying to implement an interdisciplinary treatment encompassing all traditional methodologies. It is proven that Ashwagandha rasayana (*Withania somnifera L.Dunal*) has better functions than hydroxychloroquine. The ayurvedic formulations such as Sudarshan Ghanvati and Sanshamanivati are also used. The combination of hydroxychloroquine (HCQ) and azithromycin is found to cure COVID-19 more effectively. Use of Tocilizumab is found to cure the respiratory disorders associated with COVID. Favilavir turns out to be yet another effective drug. The alternative medical system has effective prophylaxis and is considered better for the treatment of COVID-19. Ayurveda and yoga improve immunity thus maintaining good health. This review throws light on the mode of progression of the virus along with the various treatment protocols adopted to fight COVID-19. © 2020 Elsevier Ltd. All rights reserved.

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1. Introduction

SARS-CoV-2, the human coronavirus which emerged in Wuhan, China in December 2019 is affecting the entire globe, proving fatal to several millions. The SARS-CoV-2 belongs to a group of RNA viruses which predominantly cause respiratory illness in mammals and contains other lethal varieties such as severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS). It belongs to family *Coronaviridae* and order *Nidovirales* [1a]. It contains a positive sense single stranded RNA genome belonging to Baltimore classification IV. Club shaped spikes that project from the viral surface (as is evident from the microscopic images) resembles solar corona and hence the name [1b]. The crown shaped projections that are proteinaceous peplomers or glycoproteins termed as spike glycoproteins (SGPs) play a vital role in breaching host cell and initiating viral infection [2]. Several researchers all over the world are putting in tireless efforts to

develop vaccines. Although many vaccines are still being discovered and undergoing testing in many parts of the world, it will take quite some time to gain control over the pandemic. Traditional drug discovery with its time consuming nature may not prove effective since a quick and reliable curative measure is the need of the hour. Preventive, curative and rehabilitative approaches need to be adopted to manage the current situation. Integrating the modern medicine with Ayurveda turns out to be the best method to overcome the current crisis.

1.1. Mode of progression of infection and viral replication

When an infected person sneezes or coughs and thus expels virus laden droplets, coronavirus enters the nose and throat of the person it comes in contact with. Now the spike glycoproteins (SGP) of the virus infects the host cell by binding with certain receptor molecules, as shown in Fig. 1.

The nasal mucosal lining, epithelial cells of respiratory system and endothelial cells of cardiovascular system are rich in Angiotensin converting enzyme 2 (ACE-2) – a cell surface receptor [3]. Bind-

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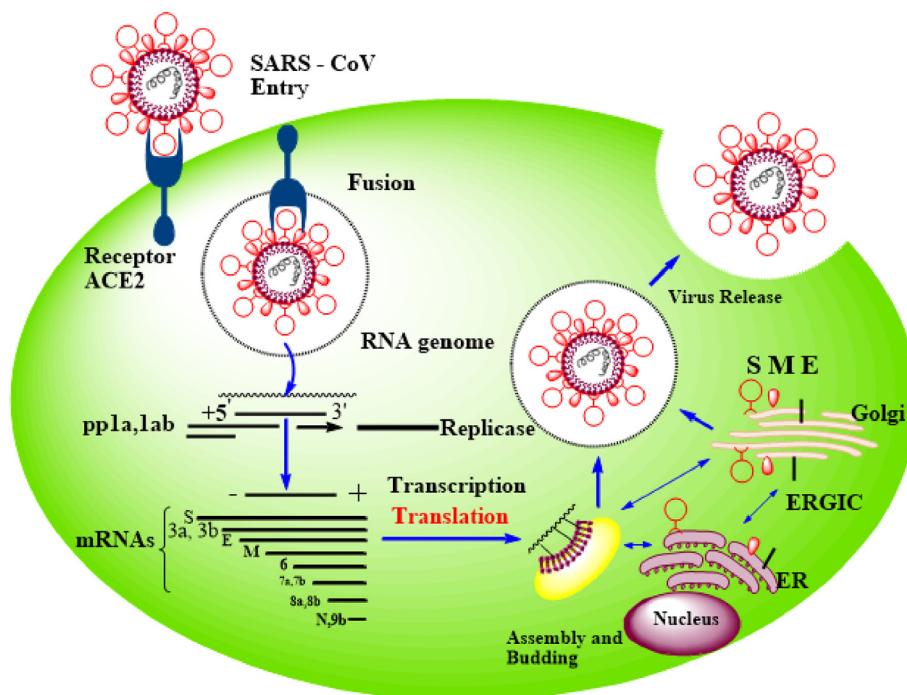


Fig. 1. Mode of progression of infection and replication of SARS – CoV-2 virus.

ing of the viral SGP specifically with ACE-2 receptor is the initial step of infection. As is evident from the figure, the binding leads to conformational changes in the receptor that facilitates successive binding of viruses to other proximal receptors. This will exponentially increase the progression of viral infection [4]. Sialic acid, a bioactive proteoglycan present in the host cell binds to viral glycoprotein named hemagglutinin (HA), which is a lectin with ligand binding domains common to all rhinoviruses [5,6]. The binding affinities of these pathogenic proteins are so high that it can easily override or block the cytokine interferon triggered immune response of the host cell. The virus now interferes with the cell replication process and starts making copies of itself and invades other cells. No symptoms are shown during the incubation period. The initial symptoms such as fever, dry cough, sore throat, loss of taste and smell etc. are exhibited by the patients once the virus makes several copies of itself by infecting numerous cells. This marks the onset of upper respiratory tract infection. If the virus is not destroyed during this initial phase it moves down the trachea into the lungs and starts attacking the alveoli and alveolar cavity. This is when the patients become critically ill [7]. The onset of lower respiratory tract infection stimulates the WBCs to wage war against virus. As a result, the alveolar oxygen transfer mechanism is interrupted. Chemokines are released by the WBCs to defeat the virus, thus leaving behind plenty of fluid and dead cells. The patient now requires oxygen support and non-invasive ventilatory support [3]. For the immunocompromised, the conditions deteriorate into acute respiratory distress syndrome (ARDS) [8] and this may be fatal. Bacterial pneumonia accompanying the viral infection also worsens the scenario. Sometimes the viral infection proceeds to a stage where systemic transmission of viruses to endothelial cells of vital organs such as kidneys, heart etc occur. When the binding of viral glycoproteins with ACE-2 of the endothelial cells of cardiovascular system occur, it will lead to increased levels of troponin 1 and creatine kinase followed by irregularities in blood pressure as the latter is involved in blood pressure regulation. This can eventually lead to cardiac arrest [9,10].

1.2. Widely used treatment methods

Varieties of antiviral drugs are used to treat COVID-19, as its viral genome shares many similarities in pathogenesis with other RNA viruses such as HIV, Ebola, influenza etc. Hence drugs like tamiflu and favilavir used against influenza, lopinavir and ritonavir used against HIV and remdesivir used against Ebola and Nipah, were also used to combat COVID-19 along with other drug formulations [11]. The following drugs were used in overcoming the viral infection in various places across the globe.

- Favilavir [12] (Fig. 2) was the first approved coronavirus drug in China. It is a pyrazine-carboxamide derivative and the mechanism of action is related to selective inhibition of viral RNA dependant RNA polymerase.
- Chloroquine phosphate [13] (Fig. 3) is an important derivative of hydroxychloroquine (HCQ) and belongs to drug class 4-aminoquinoline and inhibits virus entry into cells.
- Both chloroquine phosphate and HCQ was approved by US FDA for emergency use and resulted in 50% reduction in symptom score for patients with lower respiratory tract infection [14] and reduction in progression of upper tracheal infection to lower trachea. Unfortunately, anorexia, blurred vision, headache, diarrhoea, vomiting and cardiotoxicity has been observed as side effects of these drugs in certain patients.
- Remdesivir [15,16] (Fig. 4) is yet another drug used for treatment. It is an inhibitor of viral RNA dependant polymerase with potent activity against both SARS and MERS [17].

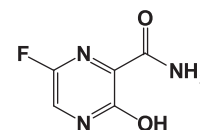


Fig. 2. Structure of favilavir.

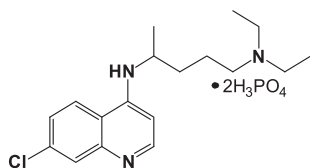


Fig. 3. Structure of chloroquine phosphate.

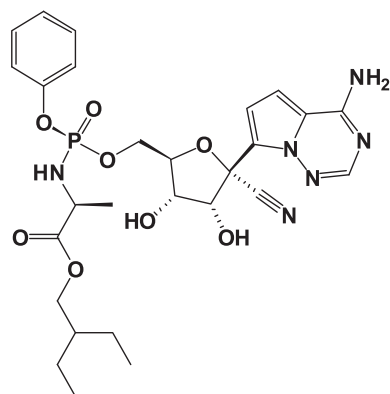


Fig. 4. Structure of remdesivir.

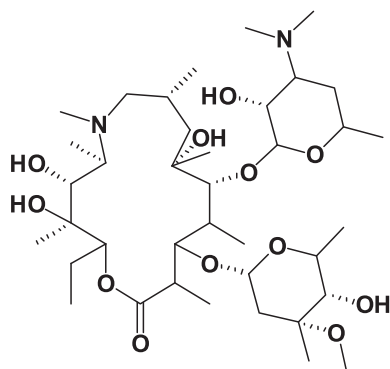


Fig. 5. Structure of azithromycin.

- Azithromycin (Fig. 5) a well-known antiviral drug in combination with hydroxychloroquine is also found to provide effective cure [18].
- Oseltamivir, an antiviral drug blocks and prevents the progression of viral infection into the respiratory tract. Xiyanning, a traditional Chinese medicine (TCM) exhibited significant clinical antiviral efficacy [19]. Use of Tocilizumab which was previously used as an immunosuppressive drug against rheumatoid arthritis and juvenile idiopathic arthritis [20] is found to cure the respiratory disorders associated with COVID-19.
- Type 1 interferons (IFN-1) [21] are a group of cytokines [22] secreted by cells upon recognizing viral components by pattern recognition receptors (PRR). IFN-1 produced will be recognized by IFNAR receptors [22] in cells and this leads to activation of Interferon stimulated genes (ISGs) [23]. They interfere with viral replication and arrest progression of disease [24]. IFN-1 also shows enhanced progress in case of patients with acute respiratory distress syndrome (ARDS). Treatment must be limited to early phase as SARS-CoV-2 induces an excessive IFN-1 mediated antiviral response leading to tissue damage. Combinations of IFN-1 with lopinavir [25], ritonavir [26] or remdesivir [27] is found to increase its efficacy.

- Fusagenix DNA vaccine developed by Entos pharmaceuticals is found to stimulate the production of B and T lymphocytes thus enhancing immunological responses [28].

1.3. Ayurveda for COVID-19 management

Even though modern anti-viral drugs are effective in treating the symptoms associated with SARS-COVID, many of them possess serious side effects. Thus, identifying suitable phytochemicals from various Ayurvedic formulations provides an effective alternative therapy to handle the current pandemic situation.

Ashwagandha [29] or *Withania somnifera* is an ancient medical herb is used in many ayurvedic formulations. Withanone and Withaferin (Fig. 6) are two antimicrobial agents present in it. As per the collaborative research conducted by IIT Delhi and AIST Japan, Withanone is found to target main protease, the main protein splitting enzyme of SARS-CoV-2 thereby interrupting viral replication. Natural products like *Tinospora cordifolia*, *Piper longum*, *Glycyrriza glabra* can enhance the immunity. Tissue rejuvenating approaches like massage, oil pulling, rasayana etc. [30,31] aid in improving the immunity. Structure-based phytochemical design studies towards spike glycoprotein and main protease have been carried out by Gopi Mohan et.al.[32]. Several ayurvedic formulations are used in the clinical management of COVID. Various studies highlighting the cellular uptake of the bioactive components and the related mechanistic aspects has been reported.[33] The most prominent part of treatment involves hindering the progression of COVID-19. The recovered patients require pulmonary rehabilitation for improving pulmonary function. Stress reduction activities and routine cardiovascular check-ups are also advised. [34] This is where meditation and yoga find its importance. Adopting yoga for community-based interventions following the rules of social distancing is highly essential. Several herbal formulations and dietary measures having immunomodulator potential can be offered by Ayurveda that can provide a cumulative effect along with the modern medicine. The ayurvedic formulations such as Sudarshan Ghanvati containing amla (*Embllica officinalis*), harad (*Terminalia chebula*) and haldi (*Curcuma longa*) as the main ingredients and Sanshamanivati consisting of giloy (*Tinospora cordifolia*) and ativisha (*Aconitum heterophyllum*) were found to cure COVID-19 effectively [35]. These formulations play dual role as preventive as well as prophylactic drugs. Ayush kwath is another ayurvedic formulation composed of medicinal plants like holy basil (*Ocimum tenuiflorum*), cinnamon (*Cinnamomum verum*), ginger (*Zingiber officinale*), black pepper (*Piper nigrum*). It was found to boost

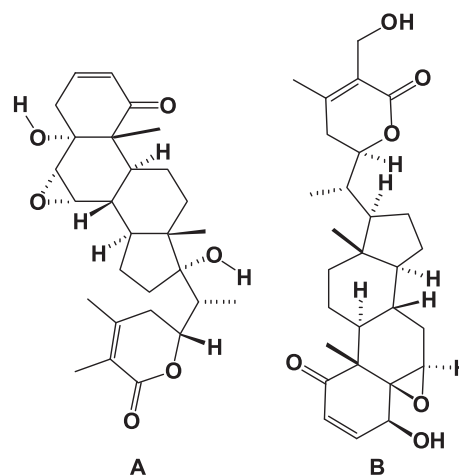


Fig. 6. Structure of (A) Withanone; (B) Withaferin A.

immunity against the corona virus. [36]. Clinical trials for prophylaxis have been initiated by Ministry of Ayush with the support of Council of scientific and industrial research (CSIR) and Indian council of medical research (ICMR). The integrative approach will generate questions, which could be answered through interventional and observational studies.

2. Conclusion

Entire world is now suffering from this unprecedented pandemic. In India the spread has been reported with 11,029,326 confirmed cases, 10,724,144 recovered cases and 156,598 deaths as of February 2021. This has invoked various disciplines of the biomedical research community to address the viral infection and propagation. Its high time that we merge our traditional system of medicine with modern medicine. Ayurveda, siddha, unani, homeopathy, yoga and naturopathy interventions has enough potential and possibilities to be used both for prevention and treatment of COVID-19. Use of these safer options needs to be adopted, however more research is certainly needed to overcome this pandemic.

CRedit authorship contribution statement

Hareesh Krishnan: Conceptualization, Writing - original draft. **M. Leema:** Conceptualization, Writing - original draft. **G.S. Gopika:** Conceptualization, Writing - original draft. **P.M. Hari Prasad:** Conceptualization, Writing - original draft. **Abhilash Rajan:** Conceptualization, Writing - original draft. **Arathy Anil:** Conceptualization, Writing - original draft. **Anandhu P. Dev:** Conceptualization, Writing - original draft. **Zeena S. Pillai:** Supervision, Writing - review & editing.

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.

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