IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Coronavirus Disease 2019 (COVID-19): A Review on the Barbaric Virus & Probable Treatments for it

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Abstract: The world was shaken by the outbreak of the recent disease due to Coronavirus. Death counts of people dying due to the disease, starting with China and spreading to other nations, losing counts; making its management difficult and the people having unavoidable symptoms and a miserable time dealing with the same, COVID-19 has undoubtedly stirred the entire human race, making them scratch their brains hard on how to fight and eradicate the pandemic. This review attempts to give a complete update on the barbaric virus, and how it emerged on to become the global threat that it is after a thorough literature search regarding the concerned topic.

Index Terms **- Coronavirus, COVID-19, MERS, SARS, SARS-CoV-2.**

I. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by a novel coronavirus which is touted to have been discovered not before than the recent times. A thorough literature search on the same revealed that "Coronaviruses are a family of viruses that cause illnesses ranging from the common cold to more severe diseases such as Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS)", as per WHO. Out of the large family of coronaviruses, SARS-CoV-2 is the seventh. The other six are SARS-CoV, MERS-CoV, HKU1, NL63, OC43 and 229E. Out of these, severe disease is caused by SARS-CoV, MERS-CoV and SARS-CoV-2, the others cause mild symptoms.[1]

II. History & Origin of the Coronavirus

It is of utmost importance to know the origin and spread of the virus considering the fact that this tiny notorious body has created such a havoc worldwide, making COVID-19 a pandemic the world fears of.

'Coronavirus', the name comes from the Latin word corona which means crown or halo. It appears to be surrounded by a solar corona having a spiked structure looking like a crown under an electron microscope. The Chinese authorities identified this novel coronavirus on January 7,2020 and since named it as SARS-CoV-2. SARS-CoV-2 (also referred to as HCoV-19) is the causative virus of this novel pneumonia (COVID-19). It is a new strain which was unidentified in humans earlier, although confirming transmission of the same from one human to another. The SARS-CoV-2 virus resembles to a *Rhinolophus affinis* bat coronavirus gene (RaTG13) by 96% at a whole genome level, whereas, upto 79.6% resemblance was found to the coronavirus that caused SARS back in November, 2002, recorded to be also originating in China.

An analysis of the SARS-CoV-2 genome conducted in order to understand how this virus could have arisen clearly manifested that SARS-CoV-2 has natural origin & is not manipulated or synthesized in a laboratory.

The RaTG13 bat sequence helped reveal key RBD mutations and the polybasic cleavage site. The receptor-binding domain (RBD) in the spike protein has six residues out of which five of them differ between SARS-CoV-2 and SARS-CoV. It has also been proved that SARS-CoV-2 binds to human ACE-2 with high affinity, but the prediction made by computational analysis suggests that there is no ideal interaction between them and that the RBD sequence is different from those shown in SARS-CoV to be optimal for receptor binding. Thus, the high affinity binding of the SARS-CoV-2 spike protein to human ACE-2 is most likely the result of natural selection on a human or a human-like ACE-2.[1]

III. Spread of the virus

The causative agent of the current COVID-19 pandemic, SARS-CoV-2, is a single stranded positive sense RNA virus that is related to severe acute respiratory syndrome coronavirus (SARS-CoV). [2]

Initially, these viruses were transmitted from animals to humans through illegally-trafficked pangolins, crossing the barriers of species. Civet cats were the ones responsible to transmit SARS to humans while, a type of camel was responsible to transmit MERS to humans. Several known coronaviruses are circulating in animals that have not yet infected humans.[3]

- **How does the virus act?**

The virus particle consists of a fatty sheath in which spike proteins are embedded, and which surrounds a strand of RNA.

The **sheath, the spike and the RNA** hold the key.

1. **The sheath**: The sheath encapsulates the viral genetic material. Alkaline environment breaks open the sheath.
2. **The spike**: The spike enables the virus to enter the host cells. The virus needs to enter human cells to replicate and spread the viral disease which cannot be done on its own. Here, the spike protein comes to its rescue and acts as the key. **The Angiotensin Converting Enzyme, ACE2, a protein** found on the surface of many cells in the human body, including **the lungs,** which is of concern for COVID-19, modulates vascular functioning, having **an important role to play in organ protection and blood pressure control**, thus being a greater cause of concern for people with hypertension during COVID-19 infections.

3. **The genetic material- RNA:** The replication-transcription complex is the key ingredient of the SARS-CoV-2 virus responsible for making more RNA copies of the virus.

- **Progression of the disease:**

There are three stages of the disease namely, **viral replication, immune response and pulmonary damage.**

As Soon as the SARS-CoV-2 enters human body, it starts invading our cells and reproducing in the upper respiratory tract and the person remains asymptomatic but can definitely spread the infection. This period lasts for about five days & is known as the prodrome period.

The immune system starts generating a response by producing antibodies and Helper T-cells, which fights the infection. In severe infection, when the immune system is still not activated, the infection worsens and reaches the alveoli; the walls of these alveoli and entirely, the lungs is damaged by the coronavirus. The damaged material lines the walls, making them thicker, and block the easy transmission of oxygen to the blood cells which leaves you breathless and with very low oxygen levels in your blood. In other cases, the viral load is so high (medical care givers), that the disease moves quicker to the air sacs than the immune system can adapt. For the proper functioning of the alveoli, they should have thin walls.

Old people, men and the unhealthy (Diabetes/Hypertension/Lung impairment/Smokers) are more susceptible to getting an infection as compared to the young, women and the healthy individuals respectively. The virus battles with the body's immune system and the native flora of human respiratory tract for spreading the infection. More the virus (called the virus load) that gets into the human body, the greater is the chances of getting the virus.

Talking about the surface, the virus is able to remain infectious on stainless steel and plastic, but stays active on cardboard for up to 24 hours. Copper doesn't let this virus survive.

IV. Comparison of COVID-19 With SARS and MERS

The pathological features of COVID-19 greatly resemble those seen in severe acute respiratory syndrome (SARS; 2002-2003) and Middle Eastern respiratory syndrome (MERS;
2012-ongoing) outbreaks.[7]
SARS was initiated by zoonotic transmission of a novel coronavirus (likely from bats via palm civets) in Guangdong Province, China whereas MERS was traced to zoonotic transmission of a novel coronavirus (likely from bats via dromedary camels) in Saudi Arabia. All 3 viral infections have common symptoms like fever and cough, which often lead to respiratory problems more fatal for patients with older age and underlying health conditions.
The World Health Organization (WHO) declared the SARS outbreak under control on July 5, 2003. A total of 8096 SARS cases and 774 deaths across 29 countries were reported for an overall CFR of 9.6% which means, SARS killed about 9 percent of those it infected.
MERS is still not contained and is responsible for 2494 confirmed cases and 858 deaths across 27 countries for a CFR of 34.4%. MERS, being the more deadly, did not spread as widely, but killed one-third of those infected.
Despite much higher CFRs for SARS and MERS, COVID-19 has led to more total deaths due to the large number of Cases.

V. Transmission, Symptoms & effects on pregnant women, old age & other vulnerable patients

Person-to-person transmission has been observed in patients affected by the Coronavirus. However, transmission of novel coronavirus that causes coronavirus disease 2019 (COVID-19) from an asymptomatic carrier with normal chest computed tomography (CT) findings has not been reported. [8]
Case-fatality rate are much higher for elderly with 14.8% in patients aged 80 years (208 of 1408) & 8.0% in patients aged 70-79 years (312 of 3918) & those with other chronic diseases already with 49.0% in critical cases (1023 of 2087) as compared to general public with 2.3% (1023 of 44 672 confirmed cases).

As per a study conducted, 9 pregnant women were observed at **Zhongnan Hospital of Wuhan University, Wuhan, China, from Jan 20 to Jan 31, 2020.** All nine patients had a caesarean section in their third trimester. The clinical characteristics of COVID-19 pneumonia in pregnant women were similar to those observed in non-pregnant adult patient. There is currently no evidence for intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in late pregnancy.[9]
The symptoms observed in these COVID-19 patients are as follows,

- fever (7)
- cough (4)
- myalgia (3)
- sore throat (2)
- malaise (2)
- Fetal distress (2)
- Lymphopenia i.e. <1 · 0 × 10^9 cells per L (5)
- Increased aminotransferase concentrations (3).

As of Feb 4, 2020, none out of the nine patients developed severe COVID-19 pneumonia or died. Nine live births were recorded. Amniotic fluid, cord blood, neonatal throat swab, and breast milk samples from six patients were tested negative for SARS-CoV-2.

Timeline of cured patients:

In these patients who recovered from COVID- 19 pneumonia, 4 stages of lung involvement were defined on CT:

1. **Early stage** (0-4 days after onset of the initial symptom): In this stage, ground glass opacities (GGO) was the main radiological demonstration distributed sub-pleurally in the lower lobes unilaterally or bilaterally. In the ochort, negative findings were revealed in four patients (total CT score=0). However, repeat pulmonary CT showed lung abnormalities in these 4 patients.
2. **Progressive stage** (5-8 days after the onset of the initial symptom): In this stage, the infection rapidly aggravated and extended to a bilateral multi-lobe distribution with diffuse GGO, crazy-paving pattern and consolidation

3. **Peak stage** (9-13 days after the onset of the initial symptom): In this stage, the involved area of the lungs slowly increased to the peak invovlement and dense consolidation became more prevalent. Findings included diffuse GGO, crazy-paving pattern, consolidation, and residual parenchymal bands.

4. **Absorption stage** (≥14 days after the onset of the initial symptom): In this stage, the infection was controlled and the consolidation was gradually absorbed. However, in this process, extensive GGO could be observed as the demonstration of the consolidation absorption. Noticeably, in this study, no crazy-paving was observed in this stage, likely as a result of recovering. Based on the total CT score, the absorption stage extended beyond 26 days (our last days of follow-up) from the onset of initial symptoms. [10]

For the following cured patients, the discharge criteria were:

1. afebrile for greater than 3 days;

2. respiratory symptoms significantly improved

3. improvement in the radiological abnormalities on chest

VI. Drugs for the treatment or management of COVID-19:

Of late, much attempts have been made by the scientists endeavouring to come up with the best treatment option for the coronavirus. Some of the drugs being touted to be successful in relieving the disease are as follows:[11]

1. **Chloroquine-Hydroxychloroquine Combination:** CQ and HCQ share similar chemical structures and mechanisms of acting as a weak base and immunomodulator. Chloroquine also affects glycosylation of angiotensin converting enzyme-2(ACE-2), the receptor that SARS-CoV-2 uses to enter cells. The virus, is thus, prevented from binding to the ACE-2 receptor. TMPRSS2 activity is essential for viral spread and inhibition of TMPRSS2 can block infection of lung cells. Hydroxychloroquine helps calm the immune response.[12,13,14]

2. **Favipiravir:** It was approved for treatment of novel influenza on February 15, 2020 in China. This drug is currently undergoing clinical trials in treating COVID-19. It is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor. Favipiravir is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, thus inhibiting RNA polymerase activity. Therefore, favipiravir may have potential antiviral action on SARS-CoV-2, which is an RNA virus. Favipiravir was reported to be more potent antiviral than lopinavir/ritonavir.[15,16]

3. **Remdesivir:** It is another potential drug for treatment of COVID-19. Remdesivir is a nucleoside analogue and a broad-spectrum antiviral. It reportedly reduced the viral load in lung tissue of mice infected with MERSCoV, thus improving lung function, and decrease pathological damage to lung tissue. SARS-CoV-2 infection was potently blocked by Remdesivir at low micromolar concentrations with a high selectivity index. [17,18]

4. **Darunavir**: It is a second-generation HIV-1 protease inhibitor. Darunavir was announced to inhibit SARS-CoV-2 infection in vitro on February 4, 2020 by Chinese researchers. Cell experiments showed that it had an inhibition efficiency of 280-fold greater than that in the untreated group, indicating significant inhibition of viral replication in vitro.[11,19]

5. **Imatinib**: It is a BCR-ABL kinase inhibitor and works as an anti-coronal by basically inhibiting the fusion of virions with the endosomal membrane.[11]

6. **Lopinavir/Ritonavir and Ribavirin:** Lopinavir is one kind of protease inhibitor used to treat HIV infection, with ritonavir as a booster. Lopinavir and/ or lopinavir ritonavir have anti coronavirus activity in vitro. In SARS treatment, it was found out that patients treated with lopinavir/ritonavir and ribavirin had lower risk of acute respiratory distress syndrome (ARDS) or death, compared to ribavirin alone.[20]

7. **Neuraminidase inhibitors (NAIs): NAIs** such as oral **oseltamivir**, inhaled **zanamivir,** and intravenous **peramivir** are recommended as antiviral treatment in influenza. It has been shown that neuraminidase inhibitors are effective for MERS-CoV infection but it hasn't been proved to be effective in the treatment of 2019-nCoV.

8. **Tolicizumab**: **Tolicizumab** is a humanized IgG1 monoclonal antibody, directed against the IL-6 receptor and commonly used in the treatment of rheumatoid arthritis. This drug acts as a potential treatment for SARS-CoV-2.

9. **Ivermectin**: An FDA-approved broad spectrum anti-parasitic agent, Ivermectin acts as a potential treatment for 2019-nCoV.

10. Some other drug types found to be effective in vitro, currently, are **fusion peptide** (EK1), **abidol**, **RNA synthesis inhibitors** (such as TDF, 3TC), **anti-inflammatory drugs** (such as hormones and other molecules), **Alpha-interferon** (e.g., 5 million units by aerosol inhalation twice per day), etc.

11. Shanghai Institute of Materia Medica and Shanghai Tech University's joint research team on performing an enzyme activity test & an *in-silico* drug screening reported 30 agents with potential antiviral activity against SARS-CoV-2 on January 25, 2020. These agents are as follows:[11]

i.	Indinavir	xi.	Maribavir	xxi.	Disulfiram
ii.	Saquinavir	xii.	Fosamprenavir	xxii.	Carmofur
iii.	Lopinavir	xiii.	Enzaplatovir	xxiii.	Shikonin
iv.	Ritonavir	xiv.	Presatovir	xxiv.	Ebselen
v.	Remdesivir	xv.	Raltegravir	xxv.	Tideglusib
vi.	Atazanavir	xvi.	Carfilzomib	xxvi.	PX12
vii.	Darunavir	xvii.	Bortezomib	xxvii.	TDZD-8
viii.	Tipranavir	xviii.	Deoxyrhapontin	xxviii.	Cyclosporin A
ix.	Abacavir	xix.	Polydatin	xxix.	Cinanserin
x.	Elvitegravir	xx.	Chalcone	xxx.	Montelukast

12. Chinese herbal medicines were also found to contain active ingredients against SARS-COV-2. These were **Rhizoma Polygoni Cuspidati** and **Radix Sophorae Tonkinensis**.[11]

13. **APN01**: **APN01 is** a physiological formulation of recombinant human Angiotensin Converting Enzyme 2 administrated i.v., made by Apieron Biologics. APN01 is made with the aim to act as a placebo for the virus, thus preventing it from binding onto human cells.[21]

14. **Convalescent plasma**: The blood plasma of the survivors of the coronavirus infected patients contains antibodies produced by the immune system against the novel coronavirus, and has shown good results in severely ill SARS-CoV-2 infected patients. [22]

15. **Extracorporeal membrane oxygenation (ECMO):** It is suitable for patients with poor results to prone position ventilation & refractory hypoxemia despite lung-protective ventilation after analysing each patient.

VII. Conclusion:

To sum up, the virus can be deadly for the elderly of the age of about 65 & above. While the children and young people are the least likely to be infected and harmed by the virus, they are not invincible and can be silent carriers of the disease, or face a mild version of COVID-19. Its been months since the researchers and the scientists have been looking for the ultimate cure for COVID-19, but hardly have they been successful in zeroing onto one perfect suitable candidate for its treatment. There have also been cases of relapse of the viral infection, making one think about the viral nature on one hand while questioning the extent of reliability of the testing kits on the other hand. Experience treating SARS, MERS or some other new influenza virus earlier make all the above mentioned drug options available. The future considerations for the treatment of COVID-19, the spike glycoprotein surface structure serves to be significant for the development of antivirals.

VIII. References:

1. Andersen, K.G., Rambaut, A., Lipkin, W.I. *et al.* The proximal origin of SARS-CoV-2. *Nat Med* **26,** 450–452 (2020).
2. Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation and Treatment Coronavirus (COVID-19), In: StatPearls [Internet]. Treasure Island (FL): StatPearls, 2020.
3. Mridula Ramesh, Coronavirus Outbreak: From Origin to spread, who it affects and the factors that may halt its progress- a primer, Firstpost, 2020.
4. Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation and Treatment Coronavirus (COVID-19), StatPearls Publishing; 2020.
5. Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation and Treatment Coronavirus (COVID-19), StatPearls Publishing; 2020.
6. XiaoweiLi, ManmanGeng, YizhaoPeng, LiesuMeng, SheminLu, Molecular immune pathogenesis and diagnosis of COVID-19, Journal of Pharmaceutical Analysis, Available online 2020
7. *Zhe Xu*, Lei Shi*, Yijin Wang*, Jiyuan Zhang et al., Lancet Respir Med* 2020 Pathological findings of COVID-19 associated with acute respiratory distress syndrome Published Online, 2020, https://doi.org/10.1016/S2213-2600(20)30076-X
8. MeiyunWang et al, Presumed Asymptomatic Carrier Transmission of COVID-19, 2020 American Medical Association, Published online 2020, https://jamanetwork.com/ on 03/21/2020

9. *Huijun Chen*, Juanjuan Guo*, Chen Wang*, Fan Luo,et al,* Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records *Lancet* 2020; 395: 809–15 Published Online 2020,https://doi.org/10.1016/S0140-6736(20)30360-3

10. ZunyouWu, Jennifer M. McGoogan; Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China, Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China., Published online 2020, https://jamanetwork.com/ on 03/21/2020

11. Liying Dong1, Shasha Hu2, Jianjun Gao1, Discovering drugs to treat coronavirus disease 2019 (COVID-19) *Drug Discoveries & Therapeutics. 2020; 14(1):58-60.*

12. Singh AK, Singh A, Shaikh A, Singh R, Misra A, Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries, *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* (2020), doi:https://doi.org/10.1016/j.dsx.2020.03.011.

13. Jia Liu1, Ruiyuan Cao2, Mingyue Xu1,3, Xi Wang1, Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro, Cell Discovery (2020) 6:16 https://doi.org/10.1038/s41421-020-0156-0

14. Robin E Ferner *honorary professor of clinical pharmacology* 1, Jeffrey K Aronson *clinical pharmacologist*, Chloroquine and hydroxychloroquine in covid-19 Use of these drugs is premature and potentially harmful, *BMJ* 2020;369:m1432 doi: 10.1136/bmj.m1432 (Published 2020)

15. Yan Gao, Liming Yan, Yucen Huang, Fengjiang Liu, Structure of the RNA-dependent RNA polymerase from COVID-19 virus, Science 2020, Published online: 2020

16. Yousuke Furuta, Brian B.Gowen, Kazumi Takahashi, Kimiyasu Shiraki, Favipiravir (T-705), a novel viral RNA polymerase inhibitor, Antiviral Research Volume 100, Issue 2, 2013, Pages 446-454, https://doi.org/10.1016/j.antiviral.2013.09.015

17. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19 [published online ahead of print, 2020]. *Travel Med Infect Dis*. 2020;101615. doi:10.1016/j.tmaid.2020.101615

18. Vityala Yethindra. (2020). Role of GS-5734 (Remdesivir) in inhibiting SARS-CoV and MERS-CoV: The expected role of GS-5734 (Remdesivir) in COVID-19 (2019-nCoV) - VYTR hypothesis. *International Journal of Research in Pharmaceutical Sciences*, *11*(SPL1), 1-6. https://doi.org/10.26452/ijrps.v11iSPL1.1973

19. Shen Lin, Runnan Shen, Jingdong He, Xinhao Li, Xushun Guo, Molecular Modeling Evaluation of the Binding Effect of Ritonavir, Lopinavir and Darunavir to Severe Acute Respiratory Syndrome Coronavirus 2 Proteases, bioRxiv 2020, doi: https://doi.org/10.1101/2020.01.31.929695

20. Hongzhou Lu, Drug treatment options for the 2019-new coronavirus (2019- nCoV), *BioScience Trends* Advance Publication,2020 DOI: 10.5582/bst.2020.01020

21. Alex Philippidis, COVID-19: Top 60 Drug Treatments in Development, Genetic Engineering & Biotechnology News VOL. 40, NO. 4 , Published Online: 2020 https://doi.org/10.1089/gen.40.04.02

22. Ian Sample, Coronavirus survivors' blood plasma could be used to fight infection, The Guardian, 2020.

23. Zhu N, Zhang D, Wang W, et al., A novel coronavirus from patients with pneumonia in China, 2019, *N Engl J Med* 2020; published online Jan 24. DOI:10.1056/NEJMoa2001017.

24. Huang C, Wang Y, Li X, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *Lancet* 2020; published online 2020. https://doi.org/10.1016/S0140-6736(20)30183-5.

25. Wong SF, Chow KM, Leung TN, et al., Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome, *Am J Obstet Gynecol* 2004; 191: 292–97.

26. Schoeman D, Fielding BC, Coronavirus envelope protein: current knowledge, *Virol J* 2019; 16: 69.

27. Zhang YZ. Novel 2019 coronavirus genome. Jan 21, 2020. http://virological.org/t/novel-2019-coronavirus-genome/319 (accessed Feb 4, 2020)

28. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses, *Nat Rev Microbiol* 2016; 14: 523–34.

29. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster, *Lancet*. 2020;395(10223):514-523. doi:10.1016/S0140-6736(20)30154-9

30. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold, *JAMA*. Published online 2020. doi:10.1001/jama.2020.0757