



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

Materials Today: Proceedings

journal homepage: www.elsevier.com/locate/matpr

Therapeutic approaches in COVID-19 followed before arrival of any vaccine

Vasundhra Sharma^a, Atul Pratap Singh^{a,*}, Ashish Pratap Singh^b

^a Department of Chemistry, Chandigarh University, Mohali, Punjab, India

^b Division of Materials Group, BARC, Mumbai 400085, India

ARTICLE INFO

Article history:

Received 8 June 2021

Received in revised form 2 August 2021

Accepted 23 August 2021

Available online 3 September 2021

Keywords:

SARS-CoV (serious intense respiratory condition Covid)

MERS (Middle East respiratory disorder Covid)

Nitric oxide (NO)

ABSTRACT

In present times covid-19 is spreading and is showing very destructive effects. It does not only affected the physical health but mental health as well as the economy of the major affected countries. Corona viruses are group of related RNA viruses. The first case of this virus was observed in China and then this virus got spread in the many countries and different strategies were made to stop the spread of this virus. Since no particular vaccine was available to cure this so different strategies were made. Due to the emergence of pandemic diseases, drug development and control strategies have been re-examined. One of the most important factors that scientists have to consider is the effectiveness of their drugs. This virus causes the respiratory tract infections which can range from mild to lethal. COVID-19 is a major cause of death in advanced countries. It is due to the absence of any particular vaccine that can effectively treat this condition. So in this review we will discuss about the therapeutic approaches followed to combat this deadly virus. Ayurveda, nitric oxide, nanoparticles and enzymes played a very important role in boosting the immunity and treatment of corona. Many herbs and some tips of using a combination of herbs proved to be very efficient while facing problems in breathing. Giving the dose of nitric oxide at some particular level and chloroquine the drug showed the antiviral activity against the virus. Developing methods to identify and contain COVID-19 is essential to successfully manage the virus. Various strains of the SARS-COV-2 were detected and were found more dangerous. The therapeutic approaches followed actually were efficient and can be used to combat the other variants also. This review focuses on the latest developments in the field of therapeutics and the strategies which were followed before any vaccine.

© 2021 Elsevier Ltd. All rights reserved.

Selection and peer-review under responsibility of the scientific committee of the Symposium on Synthesis, Characterization & Processing of Inorganic, bio and nano Materials –2021.

1. Introduction

Over the span of the latest twenty years, three distinct kinds of Covid have discontinuously crossed animal species like bats, shipped off human peoples, and caused a reliably growing erupt of a colossal degree pandemic. Recent discoveries of zoonotic organisms combine SARS-CoV and MERS-CoV, which can cause severe respiratory illness in humans. This virus is presently spreading like a pandemic in China [1]. It is a novel Covid that prompts a 2% passing rate. Covid is a respiratory ailment that can be associated with an astonishing number of conditions. It is typically

caused by a type of microorganism. Due to the nature of zoonotic pollution, covid is an ordinary wellspring of human diseases. By and by, we have no satisfactory confirmation to suggest that a specific untamed life animal is the contamination starting. A genuine examination of the viral source, progression, strategy for zoonotic transmission and infectivity, would help with thwarting further defilements [2]. In December 2019, people in Wuhan, the capital city of the Hubei district first observed an ailment which led to the respiratory condition. China described the whole matter to World Health Organization on 30th December 2019 and after this the sea markets were closed in Wuhan [3–5].

The deadly case was firstly represented on 11th of January 2020. And this spreaded vigorously in the other territories of China and reached other countries by the travelers who were coming from Wuhan. The virus started spreading quickly in all the major countries like China, Italy, USA, England, India and other parts of

* Corresponding author at: Department of Chemistry, UIS, Chandigarh University, Mohali, Punjab, India

E-mail addresses: vassusharma3091@gmail.com (V. Sharma), atulpiitd@gmail.com (A.P. Singh), ashishkaushic@gmail.com (A.P. Singh).

<https://doi.org/10.1016/j.matpr.2021.08.265>

2214-7853/© 2021 Elsevier Ltd. All rights reserved.

Selection and peer-review under responsibility of the scientific committee of the Symposium on Synthesis, Characterization & Processing of Inorganic, bio and nano Materials –2021.

the world [6]. Till 3 April 2021, 153 million cases are observed worldwide with 3.2 million deaths. Just after knowing that it is transferred from human to human, China implemented the lockdown in all the affected areas. Exceptionally, SARS-CoV-2 can be sent by individuals who are contaminated yet have no manifestations, not simply by indicative patients [7]. Worry about the possible spread of SARS-CoV-2 to family felines has risen out of a news report of contamination in a tiger in the Bronx Zoo. Ferrets can be tainted, with the intra-species transmission, and felines can likewise be contaminated and send the infection to different felines, while canines have low helplessness [8]. Be that as it may, it is obscure if any of these creatures can communicate the infection to people. The public authority of India has reported the call for research projects from its different financing sources and has set out on some significant exploration projects on COVID-19 that are pertinent to public requirements. This advances the new regions of Science and Technology with an exceptional accentuation on arising needs by giving assets to the improvement of antibodies and medications in this pandemic circumstance [9–11]. Considering this, it will turn out to be progressively important to keep up fundamental and composed endeavors between general society, clinical, business, and mechanical areas to build up a strong group of information and guarantee powerful diagnostics and treatment supply lines amidst this pandemic [12]. Henceforth, clinical research facilities assume a significant part in this emergency, adding to patient screening, finding, checking, and treatment. Thus, collaboration with different organizations, scholastics, governments, and drug organizations is unavoidably important to control the infection, battle the circumstance, and give answers for any future pandemic episodes [13]. In this survey, we expect to examine the updates of current diagnostics and restorative ways to deal with COVID-19 patients. A data was proposed to detect the death rate from the covid-19 (Fig. 1), number of deceased = $-0.00486 \times \text{Number of Recovered} + 0.04814 \times \text{Number of Infected} - 1139.7$ [14].

As quick diagnostics and improvement of immunizations and medications for this frightful infection are significant intercessions in the administration of the COVID-19 flare-up, the reports on this theme are fundamental in the current situation for the advancement of patients. We will also discuss the strategies followed to cope up with the conditions [15] (Fig. 2).

2. Discussion

1. Symptoms: Most regular clinical side effects of COVID-19 illness are dry hack, fever and windedness in most of patients. A few patients likewise experience different signs like sore throat, cerebral pain, myalgia, exhaustion and the runs [16]. In the underlying period of the infection, patients can be a febrile, just giving chills and respiratory manifestations. Albeit most cases seem, by all accounts, to be gentle, all patients have new aspiratory signs as ground-glass lung murkiness on chest X-beam [17]. Earlier the symptoms seen were fecer, cough, cold, shortness of breath but slowly loss of smell and taste also came into play [18]. A few patients were accounted for to have upper respiratory disease (URD), respective sketchy darkness in lung, diminished white platelet or lymphocyte number and expanded ALT, AST, LDH, CK-MB, CRP and ESR in these phases of contamination. Patients with serious pneumonia, experience the ill effects of intense respiratory trouble disorder (ARDS) and unmanageable hypoxaemia. n-CoV-2019 can cause extreme aspiratory disease, respiratory disappointment, alongside organ harm and brokenness [19].

If there should be an occurrence of extra-pneumonic framework dysfunctions, like confusions in hematologic and stomach related framework, the danger of sepsis and septic stun will be not kidding, bringing about impressive expansion in casualty rate [20]. The discoveries showed that the infection is gentle in most of patients (81%) and a couple of them create serious pneumonia, aspiratory edema, ARDS, or diverse organ harms with case ethical quality pace of 2.3%. In kids, disease by and large presents with a lot milder clinical side effects or even asymptomatic, contrasted and grown-up. As indicated by past examinations, pregnant ladies don't appear to have a serious sickness, while more seasoned patients are at a high danger of creating basic disease. The Case Fatality Rate (CFR) expanded in half of patients more established than 80 with a background marked by constant infections, for example, hypertension, diabetes, heart illnesses, respiratory sicknesses, cerebrovascular illnesses, endocrine framework problems, stomach related framework issues and tumors [21].

In the vast majority of cases, the reason for death is respiratory disappointment, septic stun or organ failure. Truth be told, expanded C-reactive protein (CRP) is a significant factor of debil-

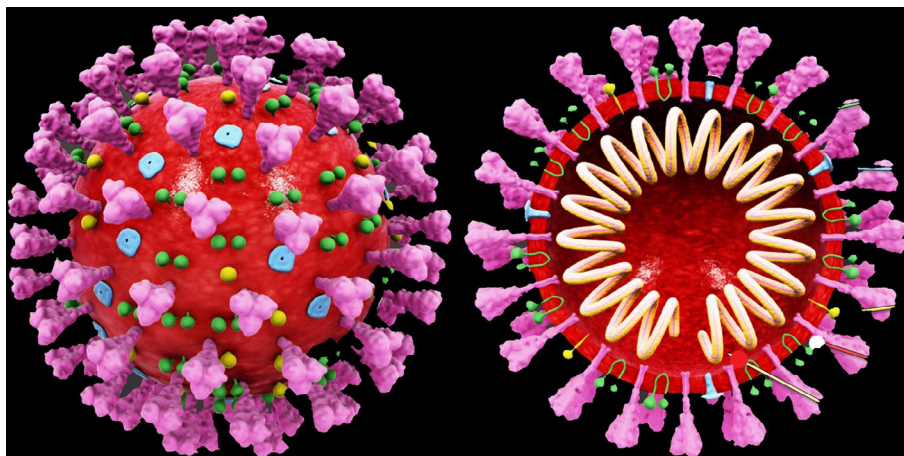


Fig. 1. Structure of Cov-19.

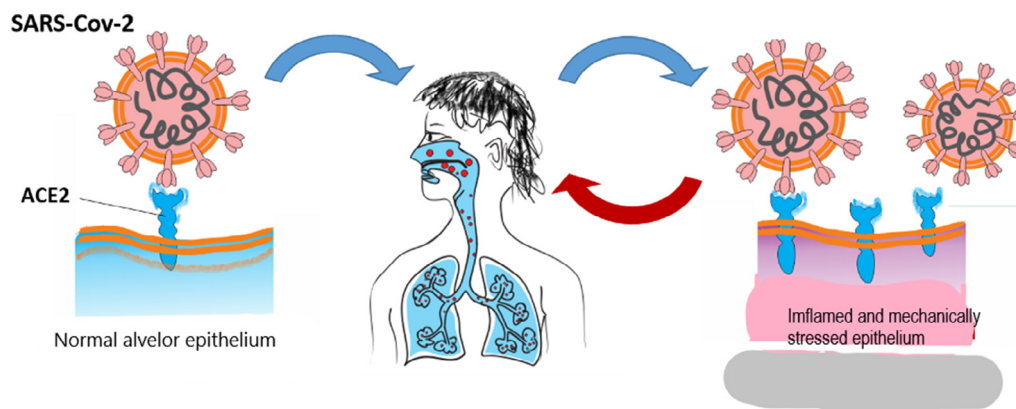


Fig. 2. Attack of virus on body.

itated insusceptibility, described by lymphopenia. Along these lines, SARS-CoV-2 is all the more likely to influence more seasoned individuals with constant infection because of their less fortunate insusceptible capacity. Corona virus has likewise been found to taint more guys (normal time of 55.5 years) than females. The less weakness of females to viral diseases is likely connected with the defensive part of X chromosome and sex chemicals, which bring about more grounded safe reaction to infection [22]. CT imaging discoveries of patients with COVID-19 uncovered that the majority of cases may show as insane clearing design, arranging pneumonia and compositional bending. On X-beams or chest CT imaging of the inspected patients, one-sided or respective contribution viable with viral pneumonia was found, and two-sided various lobular and subsegmental districts of union were seen in cases hospitalized in the emergency unit [23].

S proteins attaches to host receptor ACE2 and includes two sub units S1 and S2. S1 determines the virus host range and cellular tropism by RBD and S2 mediates virus cell membrane fusion by HR1 and HR2. M Proteins in the Fig. 3 are responsible for the trans-membrane transport of nutrients, the bud release and formation of envelope. N, E proteins and several accessory proteins, interfered with host immune response or unknown function [24].

3. Therapeutic approaches

3.1. Role of Nitric oxide

Nitric oxide is a heteronucler diatomic gas molecule. It reacts with oxygen or superoxides or free radicals and forms the nitrogen oxide compounds which directly attack on the target molecules. Till 1st December 2020 the numbers of cases were 63.3 million with a death toll of 1.47 million. Many corona virus patients are asymptomatic and which are symptomatic shows fever, dry cough, shortness of breath and malaria [25]. This also results in extreme lung injury serious desperately redness conditions and sepsis which are the enormous features of SARS and MERS. Nitric oxide (NO) can acts in two different ways i.e vasodilator and anti-inflammatory molecule. When NO acts as a Vasodilator it increases the oxygenation and decreases the pulmonary vascular resistance and when acts as an anti-inflammatory molecule it active path oxygen and remove irritants [26]. The affirmation of nitrate and nitrite in the blood of COVID-19 patients revealed that the production of NO is in a general sense higher compared to that of several individuals. Most of the critically ill patients required the ICU beds and no other thing can replace the need of Oxyegen cylinders, So a research was conducted by Harvard university and air force medical university (China) to check that the continuous inhalation of

NO can decrease the death rate and can improve oxygenation or not [27]. It was seen that by giving the dose of 80 to 40 ppm to moderate patients for complete day oxygen saturation increased by twenty percent in two days while in mild patients by giving the dose of 140–200 ppm, twenty to thirty minutes per day prevented short term respiratory status and prevented the hospitalization. A clinical report from Canada revealed that through thrombotic factors profiling, human pneumotic microvascular endothelial cells were exaggerated. So Small devices were created which can hold around 3L of NO for clinical trials and the trials were done n the people who were in contact with corona patients basically on health workers [28].

3.2. Nanoparticle-based strategies

Nanoparticles based strategies basically concentrated on the testing methods and are used in the designing of the appropriate drug. Now we are observing asymptomatic patients which are increasing day by day so a very efficient method for the testing and a vaccine which can increase the immunity is required. Nanoparticles have more for logical similarities with the virus therefore they can interact strongly with the proteins of the virus. Numerous NPs have been shown to be effective against the COVID-19 pandemic [29]. Nano technology is basically used to detect the virus in the humans. The method based on nanotechnology used to detect the virus is reverse transcription polymerase chain reaction (RT-PCR). This method is also helpful in determining the asymptomatic patients by indicating the presence of SARS cov-2 in the samples. Quantum dots which are very small in size as compared to the nanoparticles are also used in designing the vaccines for corona virus. These carbon quantum dots, blocked the viral cell entries and promoted production of ISGs [30]. The other quantum dot Ag₂S also regulated the amount of ISGs. The most common inorganic nanoparticles used in the designing of vaccine are Au nanoparticles. Au NP's can act as antigen carrier for SARS-CoV spike S protein and an adjuvant which was discovered by Sekimukai et al. in his research [31]. So nano particles played a very important role in fighting the corona virus. Due to their optical and magnetic properties these are used in forming the tets kits. Nano measured particles (40–200 nm) are particularly appropriate for focused conveyance to mucosal and alveolar constructions, mirroring normal disease courses and prompting direct safe reactions in the most noticeably terrible influenced tissues. Different NPs can be utilized to configuration drugs pointed toward upsetting the connection of SARS-CoV-2 to the ACE2 receptor and hindering the phone passage measure, while themselves remaining generally nontoxic toward the host cells [32].

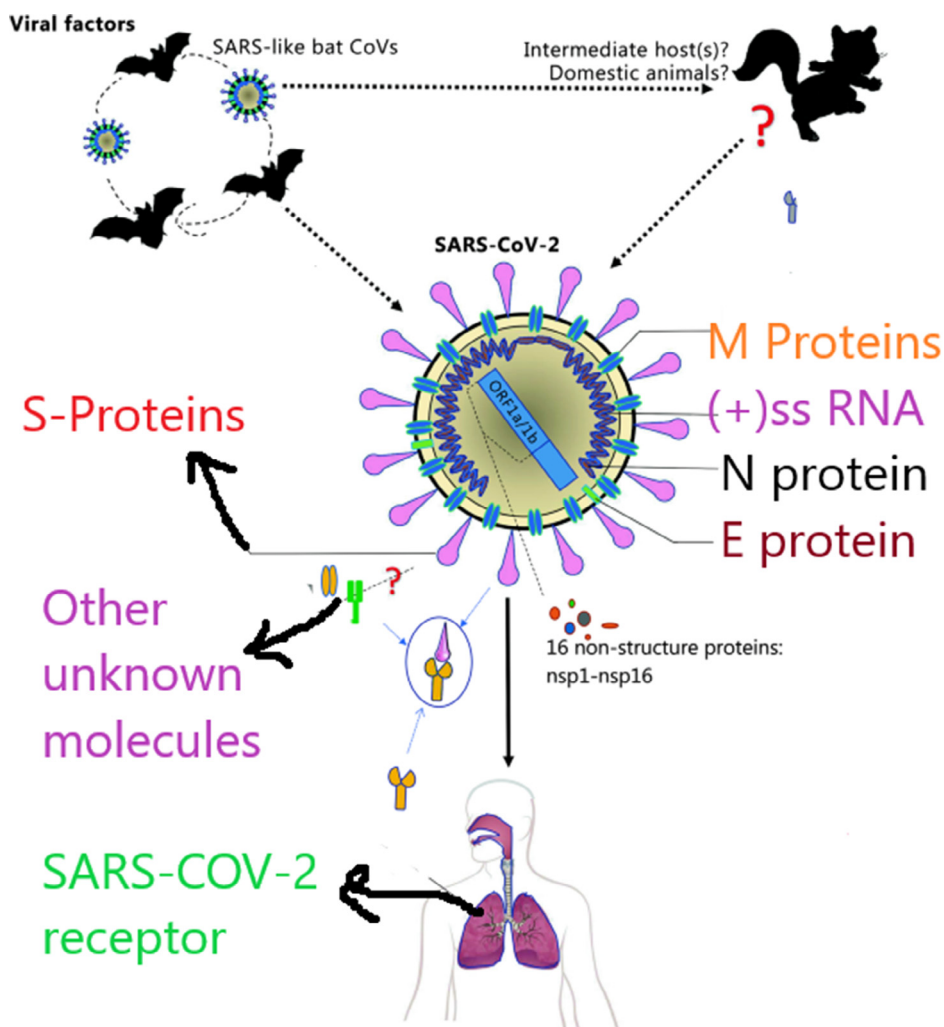


Fig. 3. Mechanism of transmembrane transport of nutrients.

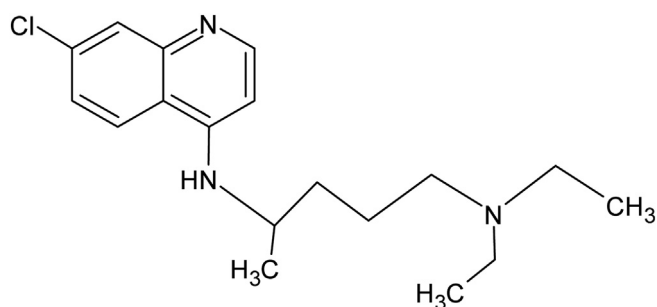


Fig. 4. Structure of Chloroquine.

3.3. Chloroquine a therapeutic drug

Chloroquine was originally developed as an aminoquinolone derivative to treat malaria. Both chloroquine and hydrochloroquine have quite similar structure which is shown in Fig. 4 and Fig. 5 respectively. The cellular mechanism of both the medicines is also similar [33]. It was approved by the USFDA in 1949 for the treatment of adults who were suffering from this disease. Its derivative, hydroxychloroquine, is also used to treat various rheumatologic conditions. Hydroxychloroquine is an anti-rheumatic drug that works by suppressing the activity of the immune system

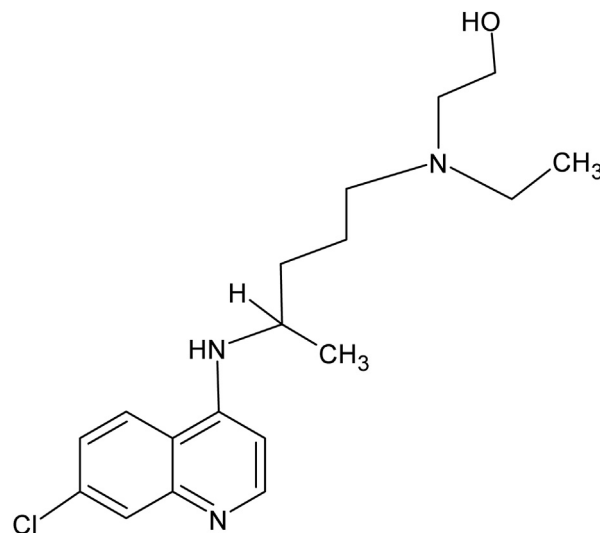


Fig. 5. Structure of hydrochloroquine.

[34]. The structure of the chloroquine and its derivative hydroxy-quine is as follows.

It can be used to treat conditions such as rheumatoid arthritis and systemic lupus erythematosus. Chloroquine is a drug that has been used to treat various infections caused by the protozoan group Plasmodium. It can also be used for the treatment of other conditions. An analysis of hydroxychloroquine and its derivatives showed that it has antiviral activity against the coronavirus co-infections, such as COVID-19. It is also used to treat pneumonia. Both hydroxychloroquine and hydroxychloroquine have shown antiviral activity against COVID-19. A study in China stated that chloroquine can reduce the duration and severity of pneumonia exacerbations, and it promotes viral-negative seroconversion [35]. Chloroquine increases the pH in the endosomes to prevent the virus particles from entering the cell. It inhibits the terminal glycosylation of an ACE2 receptor for cell entry. Due to the chloroquine's effect on the lysosomes, it can inhibit the growth of the cathepsins and cleave the SARS-CoV-2 spike protein [36].

3.4. Ayurveda

Ayurveda has emerged as the main and the very important therapeutic approach in the treatment of coronavirus. There were many companies like Patanjali and many other also which played a very important role to combat this deadly virus. Some very important Herbs played important role, many people in Himalayas use Camphor, caradamom and carom seeds as the three herb combination to get the proper amount of oxygen by smelling these herbs which when used by a corona positive patient decreased the dependence on oxygen cylinders. So these three herbs combination was effective as a therapeutic strategy in combating the virus [37]. It was also advised that drinking Kadha increases the immunity and which help to combat the virus, the main constituent for that are black paper, caradamom, tulsi leaves, cloves, ginger, turmeric etc which when boiled in water proved to be a very effective method in boosting the immunity of a person. The other thing which was followed was yoga, many postures were recommended to increase the immunity. Like kappalbhati, surya namaskaar etc. All these played a very important role [38].

It was seen in Kerala that there was a female and was suffering from the coronavirus and she had many other problems. To get cure she was sent to the Ayurvedic Centre where she recovered in 13 days even after having other problems related to lung, heart. The other thing which Indians followed was having a turmeric milk at night since turmeric has very important properties like it heals and it boosts the immunity so drinking turmeric milk also proved to be a very efficient method and was followed across the India [39]. Ayurvedic centers are not always given first priority but it helped a lot in combating this deadly virus. It was observed that in many cases even in critical stage if they started natural treatment, recovered without any life support system. Three medicines i.e. Sudarsana Churna, Talisadi Churna, Dhanwantara Gutika were given to the patients with proper diet and with advice of avoiding

Table 1
Phase1.

From Day 1 of getting corona positive to day 14		
Medicines Given	Diet Taken by the patient	Important points
Sudarsana churna (tablets)	Rice enriched with vitamin C;	Do yoga whenever feel comfortable
Talisadi churna (syrup)	Turmeric milk at night	Avoid napping in Day
Dhanwantara gutika (tablet)	Rice porridge	Take proper sleep at night

Table 2
Phase2.

From Day 14 to Day 30		
Medicines Given	Diet Taken	Important points
Vidaryadi Ghritam (syrup)	Include Ghee in the diet Eat healthy things which boosts immunity Avoid eating any junk food	Do yoga twice a day Take proper sleep at night

sleep in day time and avoiding awaking in night were recommended with this [40]. These medicines were given in a particular manner as discussed in the Tables 1 and 2.

3.5. Lockdown

When advised by World Health Organization that this virus spreads from human to human, all the countries firstly started testing at the airports and all the flights were aborted in order to stop the spread. It was noticed that the spread of this virus continued at a very large level, all the major affected countries came across a idea of complete lockdown and it was implemented. A sudden stress was created and people started hoarding the essentials. Only essential services and emergency services were allowed in the lockdown. “The lockdown was implemented in different phase and the step to stop the spread actually went well. Since people didn't came in contact with each other so the number of cases started decreasing and then different relaxations were given in the lockdown [41]. All the strategies are summarized in Table 3.

4. Virus mutation and strains

With passing each day this virus is creating more difficulties and different strains are found which are more dangerous and are not easily detected in the tests. In South Africa new variant of SARS-COV-2 is detected by the genomic scientists and they named it as 501.V2 Variant [42]. Primary analysis of this variant reveals that it spreads faster and viral load is seen high in these cases. The other mutation is N501Y, occurs in genetic sequence and is spreaded at faster rates in Britain and Australia [43]. Other variant B.1.1.7 was detected by WHO with UK authorities and is detected in Netherlands, Australia and Denmark. PC demonstrating of this strain recommends that it is 70% more contagious than other SARS-CoV-2 strains. These attributes empower this new strain to replace different strains of SARS-CoV-2. These new freak strains are introducing another worldwide danger in the COVID-19 pandemic. Variations can be recognized when every one of

Table 3
Different strategies comparison.

S. NO	Strategies	Key Features
1	Role of nitric oxide	Nitric oxide when acts as a vasodilator it increases the oxygenation which helps corona positive patients. It helped even in serious patients. [29,30]
2	Nanoparticles based strategies	These are basically used to detect the virus in the human body and are even successful in asymptomatic patients. [32–35]
3	Chloroquine	Analysis proved that chloroquine and hydrochloroquine are shows antiviral activities against corona virus. [36–38]
4	Ayurveda	Combination of three herbs proved to be efficient and combinations of medicine with proper diet successfully cured the patients. [39–42]
5	Lockdown	It helped in suppressing the spread of the SARS-COV-2 [43].

Table 4
Various strains.

Strain/ Variant Name	Detection time	Country	Key mutations
B.1.1.7	September 2020	U.K	N501Y, P681H, deleted 69–70
1.351	October 2020	South Africa	N501Y & K417N
B.1.427	November 2020	USA	L452R
B.1.1.248	December 2020	Brazil	N501Y & K417T

The Brazilian P.1, UK B.1.1.7, and South African 1.351 are very dangerous since they can escape from the immune system and can bind strongly with ACE2 receptor, can cause more harm and the therapeutic strategies which we followed for other variants may not give good results [45].

the 30,000 letters of viral hereditary code in each example are resolved utilizing particular sequencing methods. The variations D614G was the main spike protein transformation of worry that spread worldwide inside couple of months. Before the finish of June 2020, variations D614G were found in practically all the SARS-Cov-2 examples around the world [44]. The various Strains with their origin country are shown in Table 4.

5. Conclusion

COVID-19 is responsible for causing enormous number of deaths in all the major affected countries. This is particularly due to absence of a vaccine that can be used to deal with this condition. It is possible that COVID-19 is a condition where focused. If given, it may prevent the disease from developing into a more critical condition. Instead of dying, he became critically ill due to lack of oxygen. This explains why he did not become critically ill despite having been on a controlled diet and Ayurvedic intervention. Since India has one of the best ayurvedic medicines which can cure any disease without causing any major side effects so it is the best opportunity for ayurveda to overcome this disease. Lockdown also helped in avoiding spread of the virus since a proper social distancing norm were told and followed by the people these two factors helped in stopping the spread. Nitric oxide cylinders were also used and helped a lot. In all every aspect and every approach actually helped in its own way to stop the spread and to combat this deadly virus.

CRedit authorship contribution statement

Vasundhara Sharma: Conceptualization, Visualization, Writing - original draft. **Atul Pratap Singh:** Investigation, Resources, Supervision, Writing - review & editing. **Ashish Pratap Singh:** Validation, Visualization, 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.

References

- [1] WHO, <https://www.who.int/csr/don/14-january-2020-novel-coronavirus-thailand/en/>
- [2] C. Rothe, M. Schunk, P. Sothmann, et al., Transmission of 2019-nCoV infection from an asymptomatic contact in Germany, 2020.
- [3] Q. Li, X. Guan, P. Wu, et al., Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, 2020.
- [4] A.R. Fehr, S. Perlman, Coronaviruses: an overview of their replication and pathogenesis, *Methods Mol. Biol.* (2015).

- [5] R. Dijkman, L. van der Hoek, Human coronaviruses 229E and NL63: close yet still so far, *J. Formos. Med. Assoc.* (2009).
- [6] P. Zimmermann, N. Curtis, Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children, *Pediatrics* (2020).
- [7] N.C. Adusumilli, D. Zhang, J.M. Friedman, A.J. Friedman, Harnessing nitric oxide for preventing, limiting and treating the severe pulmonary consequences of COVID-19, *Nitric Oxide* (2020).
- [8] N. Takahashi et al., Clinical course of a critically ill patient with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), *J* (2020).
- [9] R. Lu, et al., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, 2020.
- [10] P. Zhou et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, *Nature* (2020).
- [11] Q. Wang et al., Structural and functional basis of SARS-CoV-2 entry by using human ACE2, *Cell* (2020).
- [12] D.H. Alamdari, et al., Application of methylene blue -vitamin C -N-acetyl cysteine for treatment of critically ill COVID-19 patients, report of a phase-I clinical trial, *Eur. J. Pharmacol.* (2020).
- [13] P. Kleinbongard, et al., Plasma nitrite reflects constitutive nitric oxide synthase activity in mammals, *Free Radic. Biol. Med.* (2003).
- [14] A.P. Singh, Model for prediction of death rate due to COVID-19 transmission and required precautions, 2020, doi.org/10.1016/j.matpr.2020.07.731.
- [15] D.D. Fraser, et al., Endothelial injury and glycocalyx degradation in critically ill coronavirus disease 2019 patients: implications for microvascular platelet aggregation, *Crit. Care Explor.* 2 (2020).
- [16] R.C. Becker, COVID-19 update: covid-19-associated coagulopathy, *J. Thromb. Thrombolysis* (2020).
- [17] A.B. Levine, D. Punihook, T.B. Levine, The role of nitric oxide and its clinical applications, *Cardiology* 122 (1) (2012) 55–68.
- [18] W. Guan, Z. Ni, Y. Hu, et al., Clinical characteristics of coronavirus disease 2019 in China, *N. Engl. J. Med.* (2020).
- [19] H. Li, Z. Liu, J. Ge, Scientific research progress of COVID-19/SARS-CoV-2 in the first five months, *J. Cell Mol. Med.* (2020).
- [20] N. Banu, S.S. Panikar, L.R. Leal, A.R. Leal, Protective role of ACE2 and its downregulation in SARS-CoV-2 infection leading to Macrophage Activation Syndrome: therapeutic implications, *Life Sci.* 256 (2020).
- [21] L. Bosca, M. Zeini, P.G. Traves, S. Hortalano, Nitric oxide and cell viability in inflammatory cells: a role for NO in macrophage function and fate, *Toxicology* 208 (2005).
- [22] J.T. England et al., Weathering the COVID-19 storm: lessons from hematologic cytokine syndromes, *Blood Rev.* (2020).
- [23] R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, et al., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, *Lancet* 395 (10224) (2020) 565–574, [https://doi.org/10.1016/S0140-6736\(20\)30251-8](https://doi.org/10.1016/S0140-6736(20)30251-8).
- [24] Q. Wang et al., Structural and functional basis of SARS-CoV-2 entry by using human ACE2, *Cell* 181 (2020) 894–904, <https://doi.org/10.1016/j.cell.2020.03.045>, e899.
- [25] F. Zheng, W. Tang, H. Li, Y. Huang, Y. Xie, Z. Zhou, Clinical characteristics of 161 cases of corona virus disease 2019 (COVID-19) in Changsha, *Eur. Rev. Med. Pharmacol. Sci.* (2020).
- [26] N. Chen, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, *Lancet* 395 (2020) 507–513, [https://doi.org/10.1016/s0140-6736\(20\)30211-7](https://doi.org/10.1016/s0140-6736(20)30211-7).
- [27] H. Long et al., D-dimer and prothrombin time are the significant indicators of severe COVID-19 and poor prognosis, *BioMed. Res. Int.* 2020 (2020) 6159720, <https://doi.org/10.1155/2020/6159720>.
- [28] E. Callaway, D. Cyranoski, China coronavirus: six questions scientists are asking, 2020.
- [29] D. Ting, N. Dong, L. Fang, J. Lu, J. Bi, S. Xiao, H. Han, Multisite Inhibitors for Enteric Coronavirus: Antiviral Cationic Carbon Dots Based on Curcumin, *ACS Appl. Nano Mater.* (2018).
- [30] H. Sekimukai, N. Iwata-Yoshikawa, S. Fukushi, H. Tani, M. Kataoka, T. Suzuki, H. Hasegawa, K. Niikura, K. Arai, N. Nagata, Gold Nanoparticle-Adjuvanted S Protein Induces a Strong Antigen-Specific IgG Response against Severe Acute Respiratory Syndrome-Related Coronavirus Infection, but Fails to Induce Protective Antibodies and Limit Eosinophilic Infiltration in Lungs, *Microbiol. Immunol.* (2020).
- [31] Mohd Ahmar Rauf, Munazzah Tasleem, Ketki Bhise, Katyayani Tatiparti, Samareesh Sau, Arun K. Iyer, Nano-therapeutic strategies to target coronavirus. *View* 2(3) (2021) 20200155. <https://doi.org/10.1002/VIW.20200155>.
- [32] L. Chen, J. Liang, An Overview of Functional Nanoparticles as Novel Emerging Antiviral Therapeutic Agents, *Mater. Sci. Eng., C* 112 (2020) 110924.
- [33] J. Liu, R. Cao, M. Xu, et al., Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro, *Cell Discov.* 6 (2020) 16, <https://doi.org/10.1038/s41421-020-0156-0>.
- [34] Chloroquine, *Drugs.com*, Accessed in March 2020. <https://www.drugs.com/pro/chloroquine.html>.
- [35] A. Zumla, J.F.W. Chan, E.I. Azhar, D.S.C. Hui, K.Y. Yuen, Coronaviruses—drug discovery and therapeutic options, *Nat. Rev. Drug Discov.* 15 (5) (2016) 327–347.
- [36] R. Kumar, J.K. Srivastava, R. Singh, et al., Available compounds with therapeutic potential against Covid-19: antimicrobial therapies, supportive care, and probable vaccines, *Front. Pharmacol.* 6 (2020) 582025, <https://doi.org/10.3389/fphar.2020.582025>.

- [37] S. Chandran, K. Dinesh, B. Patgiri, Unique contributions of Keraleeya Ayurveda in pediatric health care, *J. Ayurveda Integr. Med.* 9 (2018) 136–142.
- [38] Medical Dialogues Bureau, Kerala Plans On Using Ayurveda To Mitigate COVID-19 Spread, 2020. <https://medicaldialogues.in/state-news/kerala/kerala-plans-on-using-ayurveda-to-mitigate-covid-19-spread-64755> (accessed on 30th April, 2020).
- [39] Paul G. Auwaerter, John Hopkins ABX Guide, Coronavirus COVID-19 (SARS-CoV-2), [online] John Hopkins Medicine, last updated on 27.04.2020, accessed on 29.04.2020. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19_SARS_CoV_2_.
- [40] Priya Vrat Sharma, editor, translator of *Susruta Samhita with English translation of text and Dalhana's Commentary, Nidana sthana, Kusta Nidana:* Chapter 5, verses 33–34. Varanasi: Chaukhambha Visvabharati, First edition, 2000; page 44.
- [41] S. Kissler, C. Tedijanto, M. Lipsitch, Yonatan H. Grad, Social distancing strategies for curbing the COVID-19 epidemic, doi.org/10.1101/2020.03.22.20041079.
- [42] South Africa announces a new coronavirus variant, *The New York Times* website. <https://www.nytimes.com/2020/12/19/world/south-africa-announces-a-new-coronavirus-variant.html>.
- [43] J. Wise, Covid-19: new coronavirus variant is identified in UK, *BMJ* (2020), <https://doi.org/10.1136/bmj.m4857>.
- [44] Scientists alarmed at spread of COVID mutant, *Financial Times*. Website, <https://www.ft.com/content/a0bef737-c763-447a-b1f3-0649dc5989a0>.
- [45] J. Wise, Covid-19: new coronavirus variant is identified in UK, *BMJ* 371 (2020) m4857, <https://doi.org/10.1136/bmj.m4857>.