The New Pandemic Covid-19: Treatment Options and Developments

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Article Information

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ABSTRACT

SARS-CoV-2, the novel infectious causative factor of the new pandemic COVID-19 produced 5934936 total infected cases and 367166 death cases across multiple continents as of May 31, 2020. Majority of the world's population are still vulnerable to COVID-19. As of now, there are no clear scientific proven treatment or drug to combat covid-19, but prevention and management can reduce the spread of virus. In this crisis, a vaccine, that can train the immune system to fight against this novel coronavirus becomes essential to control the further dissemination of the new pandemic COVID-19. This review provides insights into the on- going treatment options available for COVID-19 including antiviral drugs, Ayurvedic treatment, combination of drugs and plasma therapy. This review also aims to highlight on the development of vaccines and its clinical status.

Keywords: SARS-CoV-2; anti-viral drugs; ayurvedic treatment; combination of drugs; plasma therapy; vaccines.

1. INTRODUCTION

The corona virus outbreak came to light in the end of December 2019, when the local people of Wuhan, capital city of Hubei region of china, were introduced to the clinics with severe and extreme pneumonia of an obscure cause. Huge number of primary cases were linked to Huanan

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seafood market that also traded live animals such as poultry, marmots, snakes and bats, and environmental samples from there also proved to be positive for the virus, uncovering that the virus started from the Huanan sea food market [1]. The epidemic fuelled due to movement of Chinese during Chinese New Year. The spread of infection stretched out to other provinces of China as well as to the rest of the world. The causative agent has been named as the novel corona virus or the SARS-CoV-2 and the illness is presently called as covid-19 and WHO broadcasted covid-19 a pandemic.

Coronaviridae family contains large group of viruses with single, positive strands of ribo-nucleic acid (RNA), accessible in various host species. The epic crown-like infection, otherwise called the 2019-nCoV has a place in *Nidovirales* (order), *coronaviridae* (family), *Orthocoronavirinae* (subfamily) which is divided into *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus,* and *Deltacoronavirus* [2-5]. The respiratory and enteric related ailment in animals and humans are due to *Alphacoronavirus*es and *Betacoronavirus*es. Therefore, 2019-nCov have a place within the genus *Betacoronavirus* in the subgenus *Sarbecovirus.* Although, SARS and MERS-CoV belong to *β-coronavirus* genus, the novel coronavirus also occupies the same place in the similar genus and displays distant genomic levels from that of SARS and MERS-CoV. The SARS-CoV-2 shows lower closeness (50-51.8%) with MERS CoV and comparatively higher closeness nearly 79% with SARS-CoV [6]. Compared with the SARS and MERS-CoV, the new CoV infection shows speedier human-to-human transmission, which drove the World Health Organisation to announce an overall worldwide public health emergency [7,8]. According to the latest data, up to May 31, 2020, globally 5934936 total confirmed (infected) cases, 117551 new active cases, 367166 total deaths and 4461 new deaths were accounted in the last 24h [9].

1.1 Symptoms

The most widely recognized manifestations at the onset of COVID-19 infection are fatigue, cough, headache, fever, sputum creation, diarrhoea, haemoptysis, dyspnoea (shortness of breath) and reduced levels of lymphocytes (lymphopenia) [10,11,12,13]. Abnormal features such as acute respiratory distress syndrome (ARDS), acute cardiac injury, RNAaemia and incidence of grand-glass opacities that led to death were likewise revealed [10].

1.2 Origin

Some researchers believe that the contagion is a matter of failed lab experiment and is yet a debatable topic. Andersen et al. 2020 reported that the new coronavirus is not intentionally manipulated virus and that several natural selection theories could be the reason behind. However progressively logical information could swing the parity of proof to support one theory over another [14].

However, the novel coronavirus shares 96.2% sequence identity to RaTG13 (a bat coronavirus) suspecting bat as the chief host from which the novel crown like virus started its infection. Regardless of the way that the SARS-CoV-2 started from bats, the mediator zoonotic species through which it traversed to people is yet dark and under study [15] Pangolins are the current suspects as their genome identity is closely linked to both RaTG13 and SARS-CoV-2 [16].

In tracking the global spread of the infection, by utilizing phylogenetic analysis approach on 160 full-length genomes, the recent report demonstrated that the infection advanced into three distinct clusters with the ancestral type A being the nearest to the bat genome and discovered in Americas and Europe alongside the type C, while B type being well known in East Asia. More genomic study on the causes of worldwide scattering of the infection becomes necessary [17].

2. GENOMIC CHARACTERISATION OF SARS-CoV-2

The genomic size or length of the novel crown-like virus causing the new pandemic is of 29.9 kb. The genomic RNA (gRNA) is wrapped by the phosphorylated nucleocapsid (N) protein. This nucleocapsid is covered inside the phospholipid bilayers secured by the spike glycoprotein trimmer (S), the membrane (M) protein and the envelope (E) protein in the viral envelope.[18] The novel corona virus genome is like that of other coronaviruses and contains many open reading frames (ORFs). The upstream ORF1a and ORF 1b, occupying nearly two-thirds of the gRNA, produces pp1a and pp1ab (two large polypeptides) through the process of translation, as in case of SARS-CoV and MERS-CoV, are processed into 11 non-structural proteins and 15 non-structural proteins respectively. These non-structural proteins are involved in the formation of viral replicase transcriptase complex [19]. The process of viral replication and transcription of

the gRNA is intervened by non-structural protein-12 harbouring RNA dependent RNA polymerase (RdRP) activity. The other downstream ORFs of the novel coronavirus occupying the remaining one-third of the gRNA encode for four dominant structural proteins N, E, M, S proteins and five accessory proteins (3a, 6, 7a, 7b, 8). The prediction that ORF10 exists seems to be wrong and only nine sub-genomic RNA (sgRNA) are currently predicted to make up a viral particle structure. The gRNA is bundled inside these structural proteins in order to frame virion. Transcription regulatory sequences (TRS) are motifs where leader (L)- body (B)fusion takes place. In order to make the positive-sense gRNA, the negative-sense RNA intermediates are required as templates. Thus, in the process of generating negative strands for positive strands, RdRp stops in TRS-B region, changes its template to TRS-L region, following discontinuous transcription leading to L-B fusion [19].

2.1 Lifecycle of 2019-Ncov

The spike glycoprotein containing the receptor binding domain (RBD) is known to bind to the cellular receptor. The 394-glu residue of RBD region of S-protein is recognized by the lys 31 residue on the host receptor [20]. The S protein undergoes proteolytic cleavage at (S2') position and encourages membrane fusion and viral infectivity. This is followed by receptor mediated endocytosis (clathrin- dependent and independent) [21,22]. Once the virus enters the host cell, gRNA is discharged into cytoplasm, where it produces two of the polyproteins and the structural proteins through translation, leading to the initiation of replication [23]. The formed viral particles emerge from endoplasmic reticulum-golgi intermediate compartment (ERGIC). The formed vesicles containing the virion, merge with the plasma membrane for the release of the virus (exocytosis) [24].

3. IMMUNOPATHOLOGY

Findings of SARS-CoV immunopathology may provide insights for vaccine discovery of SARS-CoV-2. When the viral antigenic peptides are presented to antigen (Ag) presenting cells (APC), body's anti-viral immunity system is activated. The virus specific B and T cells are triggered by antigen presentation, as a systemic part of humoral and cellular immunity. The antibody (Ab) production pattern of IgM and IgG are reported against 2019-nCoV. IgM antibody disappears by the end of 12th week. IgG antibody is found to play the protective role because it can last for long time [25]. The IgG Abs produced as an outcome of SARS-CoV infection are of S-specific and N- specific type of Abs [24]. The productive immune responses against the viral contamination relies mainly upon the enactment of the cytotoxic T cells, that can eventually destroy the virus infected cells. Research on cellular immunity shows severe reduction in CD4+ T cells and CD8+ T cells in peripheral blood of 2019-nCoV infected sufferers [26]. Thus, boosting the number of functional T cells becomes essential for recovery. ARDS one of the important immunopathological event caused by 2019-nCoV is due to cytokine storm [10]. When the immune system overreacts by releasing cytokines and chemokines, more than necessary, it results in cytokine storm causing inflammation. This can lead to ARDS, then multiple organ failure that eventually causes death in case of SARS-CoV-2 infected patients, very much like what happens in SARS and MERS coronaviruses [26].

3.1 Treatment

As of today. there are no clear scientifically proven treatment or drug to combat covid-19, but prevention and management can reduce the spread of virus. However, certain drugs which were effective against other viruses are under clinical trials and expected to decrease the viral load in patients. Other treatments such as ayurvedic treatment and combination of drugs can also be used to control the infection by covid-19.

3.2 Anti-viral Drugs

Though, a specific anti-viral drug has not yet identified to treat covid-19, there are certain anti-viral drugs that have been recommended. National Health Commission (NHC) of the people's Republic of China issued Guidelines for the Prevention, Diagnosis and Treatment of novel Coronavirus-induced pneumonia that was last revised on March 3, 2020 (Trail version 7) which included antivirals such as lopinavir/ritonavir, IFN-α, chloroquine phosphate, arbidol and ribavirin, immunotherapy for patients showing increased levels of IL-6, tocilizumab is suggested and other therapeutic measures include glucocorticoids and xuebijing [27]. The method of administration and dosage of those recommended by NHC is mentioned [Table 1].

Table 1. Drug names, dosage suggested for adults, routes of administration and treatment duration for the drugs included in the guidelines (version 7) for the treatment of covid-19 [27]

Drug names	Dosage suggested for adults	Routes of administration	Treatment duration
Interferon (IFN- α)	five million unit or equal dose every time, adding 2 ml of sterilized water, twice a day	Atomization inhalation of α-IFN	5-7 days
Lopinavir/ritonavir	200 mg/50 mg/pills, 2 pills every time, twice a day	Oral route	≤ 10 days
Ribavirin	Recommended to combine with IFN-α or lopinavir/ritonavir, 500 mg every time, twice or thrice a day	Intravenous infusion	≤ 10 days
Chloroquine phosphate	500 mg each time, twice a day	Oral route	3-7 days
Arbidol	200 mg every time, thrice a day	Oral route	≤ 10 days
Tocilizumab	400 mg of dose can be diluted with 0.9 % normal saline to 100 ml	Intravenous infusion	No more than two administrations
Glucocorticoids	Should not exceed the equal dose of methylprednisolone 1-2 mg/ kg/ day	Oral route	3-5 days
Xuebijing	100 ml/ time, twice a day	Intravenous infusion	≤ 10 days

IFN- α (Type I) which is an antiviral drug used to treat hepatitis generally, but it has been reported that it can inhibit SARS CoV replication *in vitro* [28]. Lopinavir/ritonavir along with other medications is used to treat HIV and has been demonstrated that it has anti-SARS-CoV and anti-MERS-CoV activity in clinical studies and *in vitro* [29,30]. Ribavirin can bind to RNA Dependent RNA Polymerase(RdRp) of SARS CoV-2 that reduces its activity and thereby virus can be removed [31]. Chloroquine was reported to inhibit the covid-19 infection at a low micromolar concentration by blocking the adhesion of viral particles to surface receptors of cells and thus, inhibits the viral cycle [32,33]. Arbidol is found to inhibit the SARS CoV-2 infection at a concentration of 10-30 µM *in vitro* [34].

Another drug called, Favipiravir was approved in China on February 15, 2020. This drug receives converted into an energetic phosphoribosylated form (Favipiravir-RTP) in cells and will become a substrate to viral RdRp as a consequence inhibiting its activity [35]. Therefore, favipiravir can potentially inhibit SARS CoV-2 and clinical trial has been commenced by Clinical Medical Research Center of the National Infectious Diseases.

Remdesivir, is another potential drug which is an adenosine analogue that targets viral RNA polymerase and inhibits its action. It was first administered intravenously to SARS CoV-2 patient by the Washington Department of Health and identified that remdesivir can act as a potential drug against covid-19 infection [36].

Besides, other antiviral drugs such as nelfinavir and galidesivir are also being investigated to treat SARS CoV-2 infection [37,38]. Besides, 3CLpro-1 (3CLpro inhibitor such as cinanserin [39] and flavonoids [40]), 2 (ACE2)-based peptides (an angiotensin-converting enzyme) and vinylsulfone protease inhibitors are also shown to have antiviral properties [41]. Also, PLP inhibitors such as diarylheptanoids, [42] type II transmembrane serine proteases (TMSPSS2) inhibitors [43] and BCR-ABL kinase inhibitor such as imatinib [44] can be other choices to fight against SARS CoV-2 infection.

3.3 Anti-inflammatory Drugs

Though antiviral drugs exist, it is necessary to support the treatment to fight against SARS CoV-2 since no specific drug is approved. Covid-19 infection induces cytokine storm that leads to acute lung injury and other organs as well, Acute Respiratory Distress Syndrome (ARDS) and death [45,46]. Hence, anti-inflammatory drugs are suggested along with antiviral drugs to reduce the viral load and multiorgan failure. Inflammatory cytokine antagonists such as JAK inhibitors, IL-1 antagonists, TNF inhibitors and IL-6 antagonist. Non-steroidal anti-inflammatory drugs such as glucocorticoids and corticosteroids are suggested to give at a very low concentration.

A recombinant human monoclonal antibody, Tocilizumab (TCZ) is a IL-6 antagonist that binds to IL-6 receptors and blocks IL-6 signalling along with its inflammatory response. A study revealed that repeated dose of TCZ can reduce cytokine storm which increases the patient recovery [47]. However, investigations should be expanded to its safety and efficacy. Sarilumab, another IL-6 receptor antagonist that is under study in double blind, randomized, phase 2/3 trial for patients who were hospitalized with severe SARS CoV-2 infection (NCT04315298) or patients suffering from multi-organ dysfunction [48]. Other monoclonal antibodies that are under clinical trials in China include bevacizumab (anti–vascular endothelial growth factor medication; NCT04275414), fingolimod (immunomodulator approved for multiple sclerosis; NCT04280588), and eculizumab (antibody inhibiting terminal complement; NCT04288713) [49].

SARS CoV-2 can invade cells through clathrin-mediated endocytosis. One of the key regulators of endocytosis is found to be AAK1 (AP2 associated protein kinase I). Thus, AAK1 inhibitors is suggested to fight against covid-19 as it can block viral entry. Baricitinib, a JAK inhibitor and has high affinity towards AAK1 can block viral entry and thereby reducing its infectivity [50].

3.4 Ayurvedic Treatment

Though several drugs have been prescribed to combat covid-19, cases are increasing day-by-day and it is mandatory to increase the immunity of individuals and support the treatment care. Ayurveda is a traditional system of medicine in India, originated 3,000 years ago. Ayurvedic treatment is a plant-based medicine where extracts of plants are used to treat diseases.

As known, covid-19 enters host cells via its spike protein receptor binding domain (RBD) by

binding to ACE2. If this interaction could be disturbed, entry of virus can be prevented thus reducing infectivity. *In silico* study was performed where Withanone, a compound from *Withania somnifera* (Ashwagandha) bound to ACE2-RBD complex in docking studies disturbing its salt bridges and reduced the electrostatic interactions thereby destabilizing the complex. Hence, *W. somnifera* could be considered as a first choice among herbs to fight against covid-19 by preventing its entry into host cells [51].

Another phytochemical compound, Tinocodiside from *Tinospora cordifolia* (Giloy) whose action is found similar to Withanone that binds to ACE2-RBD complex and can prevent viral entry [52]. Since, it is a potent immunomodulator, it can also enhance the innate immunity against SARS CoV-2 infection [53].

Myricetin and Scutellarein, flavones from *Ocimum sanctum* (Tulsi) are chemical inhibitors of SARS-CoV helicase by inhibition of ATPase activity [54]. *In silico* studies revealed that Scutellarein can bind motif B of RNA polymerase of SARS CoV-2, thereby reducing its replication and can control its growth and spread [55].

Besides, root of *Glycyrrhiza glabra* (Licorice) is found to contain antiviral property [56]. It has been observed that deaths are common in older people which signifies that their poor immune system which helps in faster spread of virus [57,32]. Hence, it is important to improve the immune system with daily supplements. The Ministry of AYUSH has recommended formulation which includes the decoction of Sunthi (*Zingiber officinale Roscoe*.), Lavanga (*Syzygium aromaticum (L.) Merr. & L. M. Perry*) and Maricha (*Piper nigrum* Linn.) [58]. This decoction will increase cell mediated and humoral responses as well as decreases the air way responsiveness and nasal congestion [59,60]. Curcumin, an active component in *Curcuma longa* (Haridra) is advisable to take with milk that blocks the release of cytokines such as IL-1, TNF-α and IL-6 which would help to fight against covid-19 [61].

3.5 Combination of Drugs

Since, a single specific drug has not been identified, combination of drugs has been explored to fight against covid-19. Viral load decrease was observed when hydroxyl-chloroquine was taken along with azithromycin [62]. Another combination of chloroquine with

remdesivir has been proved to fight against SARS CoV-2, *in vitro* [32]. *In silico* docking studies has been reported on combination of sofosbuvir with ribavirin which bound to SARS CoV-2 RNA polymerase, thus giving a choice to combat covid-19 [30]. Recently, Bangladesh medical team has investigated a new drug combination ivermectin with antibiotic doxycycline claiming that it cured all the patients who were tested covid-19 positive within four days without any adverse effects [63]. Other combination of drugs has to be explored to treat covid-19 until a specific drug is proven scientifically.

3.6 Plasma Therapy

Serum therapy was discovered by Kitasato and von Behring in 1890, where they derived serum from the rabbit immunized with diphtheria or tetanus that protected mice from related pathogenic agents. The principle of plasma therapy includes the organization of filtered blood serum from the immunized animals or humans (e.g., rabbit), that contains pertinent antibodies, serves to be passive immunizing agent against numerous diseases and envenomation circumstances [64].

Passive Immunization (PI) is a method that is used to achieve immediate immunization counter to pathogenic agents by administering antibodies specific to pathogen. It has also been shown that it is lifesaving in some infectious diseases. and, all the more as of late, has likewise indicated potential applications in cancer treatment. Despite the fact that antibiotics have to a great extent replaced the utilization of this method in bacterial diseases, PI stays as a significant method in the treatment of numerous viral infections when other explicit medications are not available [65].

On other side, active immunization requires the induction of immune response that requires time and also depends upon vaccine recipient. Therefore, passive antibody is the main method to have immediate immune response against infectious diseases to a susceptible person.

Convalescent blood products (CBP), obtained by gathering whole blood or plasma from a patient who tolerated past contamination and created humoral immunity against the pathogenic agents that cause disease being referred to, are a potential wellspring of explicit antibodies of human origin. Transfusion of CBP can kill the

pathogen and in the long run prompts its removal from the blood. There are different CBPs that have been utilized to acquire the passive immunity: [65]

- Convalescent plasma or serum
- Convalescent whole blood (CWB)
- Pooled human immunoglobulin (Ig)
- Antibodies such as monoclonal or polyclonal antibodies.
- High-titre human Ig

CP is the subject of attention, especially during the time of large-scale epidemics.

PI is effectively utilized to treat the infectious diseases. The meta-examination exhibited huge decrease in the mortality rate and viral burden in a study utilizing CP to treat severe acute viral respiratory diseases, including those brought about by related coronaviruses (SARS-CoV and MERS-CoV) [66].

3.7 Procedure

Patients with lab affirmed COVID-19 analyzed utilizing PCR technique (qRT-PCR) are appropriate to take convalescent plasma therapy and also they should fulfill following criteria:

- Diagnosed with severe pneumonia and high viral load
- The PAO2/FIO2 ration less than 300 (PAO2 is measured as mm Hg and FIO2 in fraction of inspired oxygen)
- Supported under mechanical ventilation

Enzyme linked immune sorbent assay (ELISA) and neutralizing antibody titers should be done one day before the improving transfusion of plasma. ABO blood characterizations for potential similarity of patients and donor must be checked, and each gets 2 consecutive transfusions of ABO-compatible convalescent plasma (400 mL altogether) on same day when they were gotten from the donor. The patients should be administered anti-viral drugs until viral load was found negative [67].

Donors between the age 18-60 years are chosen. Donors must be recovered from SARSCoV-2 infection and they will be asked to donate the convalescent blood plasma after written informed consent is acquired. All the donors should be consequently negative for SARS-Cov-2 and other viral infections. The donor must be well at least for 10days, with serum containing SARS-CoV-2–specific antibody titer greater than 1:1000 and the neutralizing antibody titer more than 40. About 400ml of convalescent plasma was taken by the strategy called apheresis (separation of components of blood) and plasma was quickly utilized for the transfusion around the same time [67].

3.8 Mechanism

Serum antibodies (Convalescent) induce therapeutic effect through various mechanisms. An antibody binds to a specific pathogen thereby directly neutralizing its pathogenicity, where as some of other antibody-mediated pathways, like antibody-dependent cellular cytotoxicity, complement activation, and phagocytosis, can add its therapeutic effect. Non-neutralizing antibodies associated with pathogenic but will not interfere with the ability to reproduce in vitro systems that might also contribute to the recovery (or) improvement of prophylaxis. The fact is that the management of passive antibodies offers just a short-term strategy for people with immediate immunity. This is very true for the highly infectious disease like SARSCoV-2 (COVID-19). Whether the fractioned plasma products (eg: monoclonal antibodies) or the vaccination can offer long-term therapeutic options, the only therapeutic approach is to utilize the human anti-SARS-CoV-2 plasma to have immediate effect and to prevent COVID-19 [68].

3.9 Major Challenges

Time of transfusion is more important because wrong time of CP infusion could risk in causing aggravating hyperimmune attacks. Researches proved that CP therapy found to be highly effective during initial stage of the disease progression. Thus optimal time for administrating CP on COVID-19 is a important factor [69].

It is expected that CP from recovered donors and who are 12 weeks after the onset of the disease with NAT level of at least 1: 160 is expected. In addition, due to various restrictions on the acquisition of CP, such as age, health condition, weight, informed consent, the required number of CPs, the ratio of patients recovered and those who need plasma causes deficiency in CP [69].

Table 2. Vaccine platform and clinical status of vaccine candidates [70]

Vaccine Platform	Candidate vaccine	Developers of candidate vaccine	Current clinical evaluation status
Non-Replicating Viral Vector vaccine	(i)Ad5-nCoV (ii)AZD1222 (ChAdOx1)	CanSino Biologics (china)/Beijing Ins. of Biotechnology University of Oxford	Phase 2 ChiCTR2000031781 Phase2b/3 2020-001228-32
RNA vaccine	(i)mRNA-1273 (LNP encapsulated mRNA) (ii)BNT162 (3-LNP-mRNAs)	Moderna, inc. funded by NIAID BioNTech/Fosun pharma/Pfizer	Phase 2 NCT04405076 Phase 1/2 2020-001038-36 NCT04368728
Inactivated vaccine	(i)Inactivated (ii)Inactivated (iii)Inactivated+alum (iv)Inactivated	Wuhan Institute of Biological products/ Sinopharm/Wuhan Inst of Virology Beijing Institute of Biological products/ Sinopharm SinoVac Biotech Ltd Institute of Medical Biology, Chinese Academy of Medical Sciences	Phase 1/2 ChiCTR2000031809 Phase 1/2 ChiCTR2000032459 Phase 1/2 NCT04383574 NCT04352608 Phase 1
DNA vaccine	INO-4800 (DNA plasmid vaccine with electroporation)	Inovio pharmaceuticals, Inc.	Phase 1 NCT04336410
Subunit vaccine	NVX-CoV2373 (recombinant np tech with matrix M adjuvant	Novavax funded by CEPI	Phase 1/2 NCT04368988

Abbreviation: NIAID refers to National Institute of Allergy and Infectious Diseases; LNP denotes Lipid nano particles; np tech denotes nanoparticle technology; CEPI denotes Coalition for Epidemic Preparedness Innovation

4. VACCINES

The world's population is still vulnerable to covid-19 due to SARS-CoV-2. Thus, developing a candidate vaccine, which can train the immune system in order to fight against the virus becomes essential. Vaccine development is a tedious, long procedure which is time consuming and also involves huge sums of money. The SARS-CoV-2 vaccine research and development is happening at pandemic speed with 10 candidate vaccines already in clinical evaluation (Table 2). The remaining 121 candidate vaccines in pre-clinical evaluation as of 30 May, 2020 is available from WHO [70].

4.1 Whole Virus Vaccine

Classic strategy for viral vaccines involves the live-attenuated or inactive whole virus type of vaccines. Codagenix/serum institute of India has developed codon deoptimized live attenuated vaccines for SARS-CoV-2 which is in pre-clinical evaluation. Other inactivated candidate vaccines in clinical phase are listed in the Table 2. Whole virus vaccines provide an advantage of natural and essential immunogenicity and ability to stimulate pattern recognition receptors (PRR). The PRR includes toll-like receptors (TLRs) such as TLR 3, TLR 7/8, and TLR 9 that can recognize molecules from the virus. However, in order to break the challenges concerning live attenuated vaccine (LAV), the viral vaccine, extensive additional testing is required to affirm its risk of Th2-mediated immunopathology and its safety level [71].

4.2 Subunit Vaccine

Subunit vaccine relies on elicitation of immune responses against S-protein and prevent its docking with human receptor ACE2 [71] Some of the protein subunit (S-protein) vaccine in pre-clinical evaluation are developed by WRAIR/USAMRIID, EpiVax/ Univ. of Georgia, Sanofi Pasteur/GSK. The Novovax vaccine candidate (NVX-CoV2373) is developed from sequences of SARS-CoV. The vaccine development utilized recombinant nanoparticle technology to obtain S-protein based antigen. The saponin-based matrix-M adjuvant was used to elicit higher levels of neutralizing antibodies and is in clinical phase1/2 evaluation [70]. Clover Biopharmaceuticals/GSK funded by CEPI (Coalition for Epidemic Preparedness Innovation) developed protein-based (S- trimer) Covid-19 vaccine candidate utilising Trimer-Tag® technology [72] is under pre-clinical evaluation. RBD based vaccine, minimises host immune-potentiation and becomes a potential target for subunit vaccine [71] Baylor College of Medicine, Biological E Ltd, Neovii/Tel Aviv University has developed RBD based vaccines and are in pre-clinical evaluation [70].

4.3 Nucleic Acid Vaccine

Nucleic acid vaccine is the novel approach to immunisation that uses DNA plasmid and mRNA sequences. The mRNA-based vaccine targeted to the S protein of SARS-CoV-2 works by active immunization. This technique uses mRNA sequence of the target protein that only recombine mRNA of the S protein *in vitro* according to the gene sequence, which is coated with lipid nanoparticles (LNPs) for effective delivery. Once injected into the muscle, the myocytes take up the LNPs and then release the mRNAs into the cytoplasm for translation into the S proteins. These endogenously synthesized S proteins will be secreted to activate both humoral and cellular immune responses [73]. Such mRNA vaccines developed by Moderna and BioNtech/ Pfizer are in human trail clinical phase evaluation for COVID-19. The non-replicating viral vector vaccine technology platform are developed by CanSino Biologics (Ad5-nCoV) and University of Oxford (ChAdOx1/AZD1222) using weakened virus (adenovirus) are also under human trial clinical phase evaluation.

5. MANAGEMENT

Though drugs and vaccines are under clinical trials, it is important for a healthy individual to increase their immune system and fight against covid-19 which might prevent spread of infection. It is recommended that healthy individual should take lot of citrus fruits, dry fruits such as walnuts, almonds and dates) in order to improvise their immune system. Otherwise suggested not to take any narcotic products and to avoid smoking. Regular workouts, enough sleep and not being stressful can also boost the immune system. However, it is recommended for elderly population and infected patients to consume vitamin, zinc and iodine supplements with the consultation of clinicians to enhance their immune system and fight against covid-19.

6. CONCLUSION

Most of the global population are still susceptible to the new pandemic. In this health crisis, there

are no clear treatment recommended to combat covid-19. Utilizing the serum of recuperated patients might be useful in the present moment until authoritative and powerful medications are found. Currently several research groups across continents are working on COVID-19 candidate vaccines and their clinical evaluation seems to be promising. Until, the invention of particular vaccine or drug or treatment, it is recommended to follow the guidelines and use combination of treatments to fight against covid-19 infection.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan China: the Mystery and the Miracle. J Med Virol. 2020;25678

2. Drosten C, Günther S, Preiser W, Van Der Werf S, Brodt, HR, Becker *et al*. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 2003;348:1967-1976.

3. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication and pathogenesis. J Med Virol. 2020;92:418-423.

4. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-733.

5. de Groot R J, Baker S, Baric R, Enjuanes L, Gorbalenya A, Holmes, et al. Family coronaviridae. Virus Taxonomy. 2012;806-28.

6. Malik YS, Sircar S, Bhat S, Sharun K, Dhama K, Dadar, et al. Emerging novel coronavirus (2019-nCoV)—current scenario, evolutionary perspective based on genome analysis and recent developments. Vet Quart. 2020;40:68-76.

7. Chan JFW, Yuan S, Kok KH, To KKW, Chu H, Yang, 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;395:514-523.

8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-513.

9. World Health Organization. Coronavirus disease (COVID-19) 2020: Situation report. 2019;132.

10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.

11. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J; 2020.

12. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019□nCoV) in Wuhan, China. J Med Virol. 2020;92:441-447.

13. Carlos WG, Dela Cruz, CS, Cao B, Pasnick S, Jamil S. Novel wuhan (2019-nCoV) coronavirus. Am J Respir Crit Care Med. 2020;201:P7-8.

14. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med. 2020;26:450-452.

15. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270-3.

16. Zhang T, Wu Q, Zhang Z. Probable pangolin origin of 2019-nCoV associated with outbreak of COVID-19. Curr Biol; 2020.

17. Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-CoV-2 genomes. Proc Natl Acad Sci. 2020;117:9241–9243.

18. Wu F, Zhao S, Yu B, Chen YM, Wang W, Hu, et al. Complete genome characterisation of a novel coronavirus associated with severe human respiratory disease in Wuhan, China. bio Rxiv; 2020.

19. Kim D, Lee JY, Yang JS, Kim JW, Kim VN, Chang H. The architecture of SARS-CoV-2 transcriptome. Cell in press; 2020.

20. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94: e00127-20.

21. Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G, Jiang C. SARS coronavirus entry into host cells through a novel clathrin-and

caveolae-independent endocytic pathway. Cell Res. 2008;18:290-301.

22. Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: A peptidase in the renin–angiotensin system, a SARS receptor, and a partner for amino acid transporters. Pharmacol Therapeut 2010;128:119-28.

23. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis, Nat Rev Microbiol. 2009;7: 439-50.

24. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: Recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14:523-534.

25. Li G, Chen X, Xu A. Profile of specific antibodies to the SARS-associated coronavirus, N Engl J Med. 2003;349:508-09.

26. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8:420-2.

27. National Health Commission of the people's republic of China. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial version 7).
Available:http://en.nhc.gov.cn/2020-03/29/c_78469.htm
(Accessed March 29, 2020)

28. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006;3:e343.

29. Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004;59:252-256

30. Momattin H, Al-Ali AY, Al-Tawfiq JA. A Systematic review of therapeutic agents for the treatment of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Travel Med Infect Di. 2019;30:9-18.

31. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci. 2020;117477.

32. Wang LF, Lin YS, Huang NC, Yu CY, Tsai WL, Chen, et al. Hydroxychloroquine-inhibited dengue virus is associated with host defense machinery. J Interferon Cytokine Res. 2015;35:143-156.

33. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res. 2020;30:269-271.

34. Arbidol and Darunavir can effectively inhibit coronavirus.
Available:http://www.sd.chinanews. com/2/2020/0205/70145.html
(Accessed February 21, 2020) (In Chinese)

35. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. P Jpn Acad B-Phys. 2017;93:449-463.

36. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382:929-936.

37. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature Rev Drug Discov. 2020;19:149-150.

38. Xu Z, Peng C, Shi Y, Zhu Z, Mu K, Wang X, Zhu W. Nelfinavir was predicted to be a potential inhibitor of 2019-nCov main protease by an integrative approach combining homology modelling, molecular docking and binding free energy calculation. BioRxiv; 2020.

39. Chen L, Gui C, Luo X, Yang Q, Günther S, Scandella, et al. Cinanserin is an inhibitor of the 3C-like proteinase of severe acute respiratory syndrome coronavirus and strongly reduces virus replication *in vitro*. J Virol. 2005;79:7095-7103.

40. Jo S, Kim S, Shin DH, Kim MS. Inhibition of SARS-CoV 3CL protease by flavonoids. J Enzym Inhib Med Ch 2020;35:145-151.

41. Liu W, Morse JS, Lalonde T, Xu S. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019☐nCoV. Chembiochem. 2020;21: 730-38.

42. Park JY, Jeong HJ, Kim JH, Kim YM, Park SJ, Kim, et al. Diarylheptanoids from *Alnus japonica* inhibit papain-like protease of severe acute respiratory syndrome coronavirus. Biol Pharma Bull 2012;35: 2036-042.

43. Hoffmann M, Kleine-Weber H, Krüger N, Mueller MA, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. BioRxiv; 2020.

44. Coleman CM, Sisk JM, Mingo RM, Nelson EA, White JM, Frieman MB. Abelson kinase inhibitors are potent inhibitors of

severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus fusion. J Virol 2016; 90:8924-8933.

45. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. In Seminars in immunopathology, Springer Berlin Heidelberg. 2017;39:529-539.

46. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, & Manson JJ. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020;395: 1033-1034.

47. Luo P, Liu Y, Qiu L, Liu X, Liu D, & Li J. Tocilizumab treatment in COVID☐19: A single center experience. J Med Virol 2020;1-5.

48. Sanofi and Regeneron begin global Kevzara (sarilumab) clinical trial program in patients with severe COVID-19. Available:http:// www.news.sanofi.us/2020-03-16-Sanofi-andRegeneron-begin-global-Kevzara-R-sarilumabclinical-trial-program-in-patients-with-severeCOVID-19 (Accessed March 18, 2020)

49. ClinicalTrials.gov. Available:https://clinicaltrials.gov/ (Accessed March 18, 2020)

50. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Stebbing J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet (London, England). 2020;395:e30.

51. Varshney A, Balkrishna A, & Singh J. Withanone from *Withania somnifera* May Inhibit Novel Coronavirus (COVID-19) Entry by Disrupting Interactions between Viral S-Protein Receptor Binding Domain and Host ACE2 Receptor. BMC virology; 2020.

52. Sagar V, Kumar AH. Efficacy of Natural Compounds from Tinosporacordifolia against SARS-CoV-2 protease, Surface Glycoprotein and RNA Polymerase. BEMS Reports. 2020;6.

53. Gupta PK, Chakraborty P, Kumar S, Singh PK, Rajan MGR, Sainis KB, Kulkarni S. G1-4A, a polysaccharide from *Tinospora cordifolia* inhibits the survival of Mycobacterium tuberculosis by modulating host immune responses in TLR4 dependent manner. PLoS One. 2016;11: e0154725

54. Yu MS, Lee J, Lee JM, Kim Y, Chin YW, Jee, et al. Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorg Med Chem Lett. 2012;22: 4049-4054.

55. Balkrishna, A. Indian Traditional Ayurvedic Treatment Regime for Novel Coronavirus, COVID-19; 2020.

56. Wang L, Yang R, Yuan B, Liu Y, Liu C. The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. Acta Pharm Sin B. 2015;5:310-315.

57. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med. 2020; 382:1199-07

58. Carrasco FR, Schmidt G, Romero AL, Sartoretto JL, Caparroz☐Assef SM, Bersani☐Amado CA, Cuman RKN. Immunomodulatory activity of *Zingiber officinale* Roscoe, *Salvia officinalis* L. and *Syzygium aromaticum* L. essential oils: evidence for humorand cell☐mediated responses. J Pharm Pharmacol. 2009;61: 961-967.

59. Kim SH, Lee YC. Piperine inhibits eosinophil infiltration and airway hyperresponsiveness by suppressing T cell activity and Th2 cytokine production in the ovalbumin☐induced asthma model. J Phar Pharmacol. 2009;61:353-359.

60. Bui TT, Fan Y, Piao CH, Van Nguyen T, Shin DU, Jung, et al. Piper Nigrum extract improves OVA-induced nasal epithelial barrier dysfunction via activating Nrf2/HO-1 signaling. Cell Immunol. 2019;104035.

61. Sordillo PP, Helson L. Curcumin suppression of cytokine release and cytokine storm. A potential therapy for patients with Ebola and other severe viral infections. *in vivo*. 2015;29:1-4.

62. Gautret P, Lagier JC, Parola P, Meddeb L, Mailhe M, Doudier, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob. 2020:105949.

63. Ivermectin with antibiotic doxycycline works to treat covid-19 patients. Available:https://www.firstpost.com/health/bangladesh-medical-team-says-ivermectin-with-antibiotic-doxycycline-works-to-treat-covid-19-patients-8381321.html (Accessed March 19, 2020)

64. Hifumi T, Yamamoto A, Ato M, Sawabe K., Morokuma K, Morine, et al. Clinical serum therapy: Benefits, cautions and potential

applications. The Keio J Med. 2017;2016-0017.

65. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, Grazzini G. Convalescent plasma: New evidence for an old therapeutic tool?. Blood Transfusion. 2015;14:152.

66. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim *et al*. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect. 2015; 211:80-90.

67. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan *et al*. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. Jama. 2020;323:1582-1589.

68. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters *et al*. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest; 2020.

69. Zhao Q, He Y. Challenges of convalescent plasma therapy on COVID-19. J Clin Virol. 2020;104358.

70. World Health Organization. Draft landscape of Covid-19 candidate vaccines. Available:https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines
(Accessed May 30, 2020)

71. Jiang S, Bottazzi ME, Du L, Lustigman S, Tseng CT, Curti E, et al. Roadmap to developing a recombinant coronavirus S protein receptor-binding domain vaccine for severe acute respiratory syndrome. Expert Rev Vaccines. 2012;11:405–13.

72. Clover Biopharmaceuticals. Clover initiates development of recombinant subunit-trimer vaccine for Wuhan coronavirus (2019-nCoV); 2020.

73. Wang F, Kream RM, Stefano GB. An evidence based perspective on mRNA-SARS-CoV-2 Vaccine Development. Medical Science Monitor. Med Sci Monit. 2020;26:e924700-1.

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