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REVIEW ARTICLES

COVID-19: Mutated Strain, Treatment Options and Vaccine Development

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COVID-19: Mutated Strain, Treatment Options and Vaccine Development

SUMMARY

The ongoing outbreak of the COVID-19 is a significant threat to global health and the economy. This disease is a highly contagious pathogenic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus has a high reproduction rate, due to that it is highly transmittable and has turned into a catastrophe. Scientists and researchers worldwide are exaggerating every possible approach to limit the spread of this malicious disease. An abrupt rise has been reported in the number of cases due to newly mutated strains like SARS-CoV-2 VUI 2020/12/01. To date, no specific drug is effective in the complete eradication of this dangerous disease but, some broad-spectrum antivirals such as Remdesivir and Lopinavir are being used in the management of this ailment. Also, every possible effort has been made in the development of vaccines for preventing the outbreak of this deadly virus. The BNT162b2 by Pfizer and m-RNA-1273 by Moderna have been recently launched into the market, which have shown undesirable effects in geriatrics leading to mortality. In this review, we have tried to highlight important aspects of the COVID-19 that will aid in global awareness and will help the researchers to investigate possible ways to eradicate this menace and design new moieties for its effectual management.

Key Words: *COVID-19, SARS-CoV-2, Mutations, Spike protein, Pandemic, Vaccine.*

COVID-19: Mutasyona Uğramış Tür, Tedavi Seçenekleri ve Aşı Geliştirme

ÖZ

Devam eden COVID-19 salgını, küresel sağlık ve ekonomi için önemli bir tehdittir. Bu hastalık, şiddetli akut solunum sendromu koronavirüs 2'nin (SARS-CoV-2) neden olduğu oldukça bulaşıcı bir patojenik hastalıktır. Virüs yüksek bir üreme oranına sahiptir, bu nedenle yüksek oranda bulaşabilir ve bir felakete dönüşmüştür. Dünya çapındaki bilim adamları ve araştırmacılar, bu kötücül hastalığın yayılmasını sınırlamak için mümkün olan her yaklaşımı fazlasıyla kullanıyorlar. SARS-CoV-2 VUI 2020/12/01 gibi yeni mutasyona uğramış suşlar nedeniyle vaka sayısında ani bir artış bildirilmiştir. Bugüne kadar, bu tehlikeli hastalığın tamamen ortadan kaldırılmasında spesifik bir ilaç etkili olmamıştır, ancak bu rahatsızlığın tedavisinde Remdesivir, Lopinavir gibi bazı geniş spektrumlu antiviraller kullanılmaktadır. Ayrıca, bu ölümcül virüsün ortaya çıkmasını önlemek için aşıların geliştirilmesinde mümkün olan her türlü çaba gösterilmiştir. Geriatride ölüme yol açan istenmeyen etkiler gösteren Pfizer'ın BNT162b2'si ve Moderna'nın m-RNA-1273'ü, yakın zamanda piyasaya sürülmüştür. Bu derlemede, küresel farkındalığa yardımcı olacak ve araştırmacıların bu tehdidi ortadan kaldırmanın olası yollarını araştırmasına ve etkin yönetimi için yeni parçalar tasarlamasına yardımcı olacak COVID-19'un önemli yönlerini vurgulamaya çalıştık.

Anahtar kelimeler: *COVID-19, SARS-CoV-2, Mutasyonlar, Spike protein, Pandemi, Aşı.*

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INTRODUCTION

COVID-19 has become a global emergency that has drastically affected the health and the economy worldwide. The rampant spread of this life-threatening havoc has given sleepless nights to the masses and authorities. Humankind is at stake and scientists everywhere are scrambling to eradicate the root cause of this disease. COVID- 19 is a deadly viral disease that has abducted many lives and the livelihood of human beings. The virus causing this disease is severe acute respiratory syndrome virus 2, i.e., SARS-CoV-2. The antigen was initiated from the seafood and wet animal market in Wuhan, Hubei, China, in December 2019, where bats, raccoon dogs, palm civets, snakes, and other animals are peddled (Bogoch et al., 2020; Lu et al.,2020). After this, numerous cases of pneumonia were observed with unfamiliar etiology. Later, reports from the deep sequencing analysis of the lower respiratory tract indicated the outbreak of a novel coronavirus and was named as COVID-19. Different states and territories have been infected with COVID-19 in the USA, China, Russia, Italy, Iran, Japan, India, etc., tolling about 76 million patients with more than 1.69 million deaths worldwide. The United States alone has confirmed at least 17.4 million cases in total, which is the highest count in the world. Looking at the current scenario, the World Health Organization [WHO] has declared it an emergency of international concern. This makes it an issue of high alert and hence builds surgency for public awareness. This article is an aid for controlling the present outbreak and future spread of COVID-19. In this review, complete detail about the viral mechanism, transmission, symptoms, mutated strains, diagnosis, various treatment options, and vaccine development landscape for coronavirus disease worldwide has been assimilated.

Phylogenetic Study

Coronavirus has been classified as a member of the Coronaviridae family, Orthocoronavirinae subfamily in the Nidovirales order (Zhu, 2019). The name coronavirus was derived from the crown-like spike proteins outlying the surface of the virus. The Coronavirus is enveloped, positive-sense, single-stranded RNA virus with size approximately equal to 20 nm. They are subdivided, based on genotypic and serological characters, into four genera: Alpha, Beta, Gamma, and Deltacoronavirus (Lefkowitz, 2018; Sexton, 2016; Su, 2017). Major species known to cause infections in humans include the highly pathogenic SARS-CoV and middle east respiratory syndrome [MERS] coronavirus and less rancorous species that include NL63, 229E, OC43, and HKU1. Like SARS-CoV and MERS-CoV, this newly emerged SARS-CoV-2 virus also belongs to the B lineage of the β-CoVs. The phylogenetic studies showed that the genome of this virus has an 80% resemblance to the SARS-CoV and 50% resemblance to the MERS-CoV (Lu et al., 2020; Ren et al., 2020).

Key Features of the Mechanism of Action of SARS-CoV -2

SARS-CoV-2 has a typical coronavirus structure, which encodes four structural proteins, i.e., nucleocapsid [N] protein, membrane [M] protein, spike [S] protein, and envelope [E] protein, and also several non-structural proteins. The process of viral entry and replication is depicted in Figure 1 (Bhoopathi et al., 2020).

The spike proteins outlying the virus's surface bind to angiotensin-converting enzyme 2 [ACE 2] receptors residing on the surface of the host cells, and fusion takes place between the viral and the cellular membranes (Belouzard et al., 2012). The protease enzymes transferrin and furin present in the host cell break the spike protein and release the viral RNA. The accomplishment of these steps leads to translation followed by RNA replication. The next step is the synthesis of structural viral proteins, M, S, and E, in the cytoplasm, embedded in the endoplasmic reticulum. Later, it is transferred to the endoplasmic reticulum-Golgi intermediate compartment, which serves as a site for coronavirus particle assembly (Song et al., 2004). At last, the formed vesicle is released through the process of exocytosis.

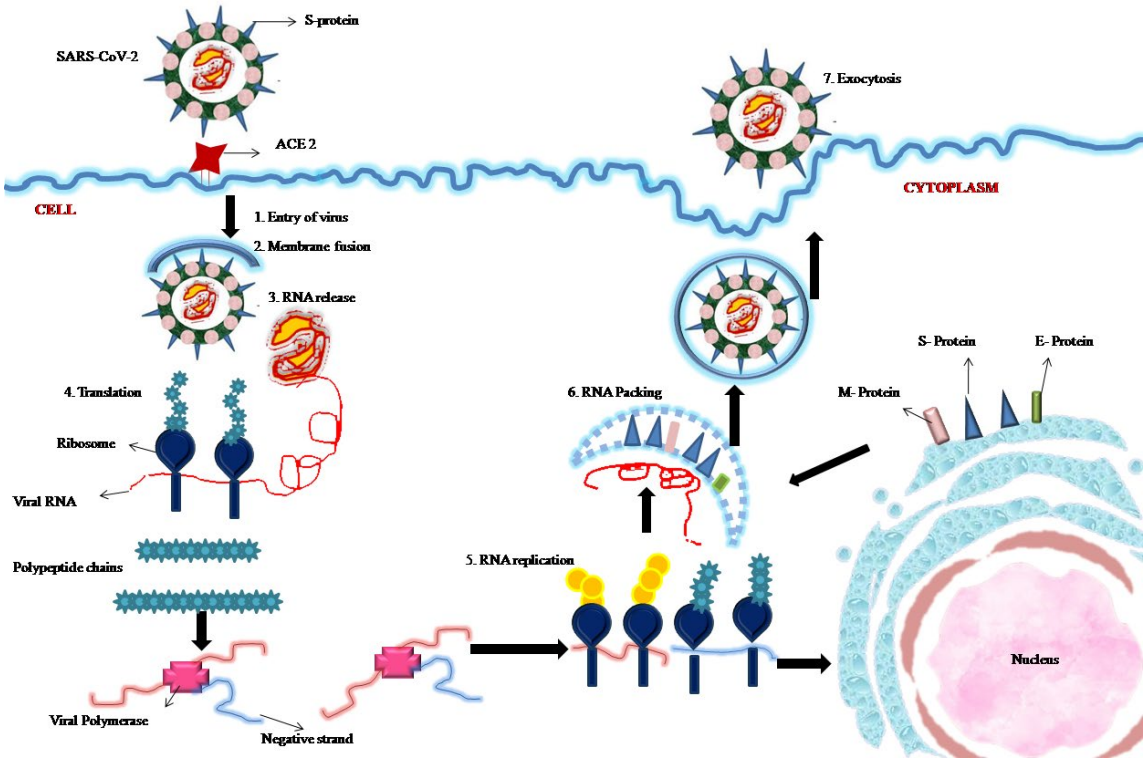

Figure 1. Mechanism of action of SARS-CoV-2

Primary Reservoir and Mode of Transmission of Coronavirus

As depicted in Figure 2, both SARS-CoV and MERS-CoV are zoonotic pathogens emerging from animals.

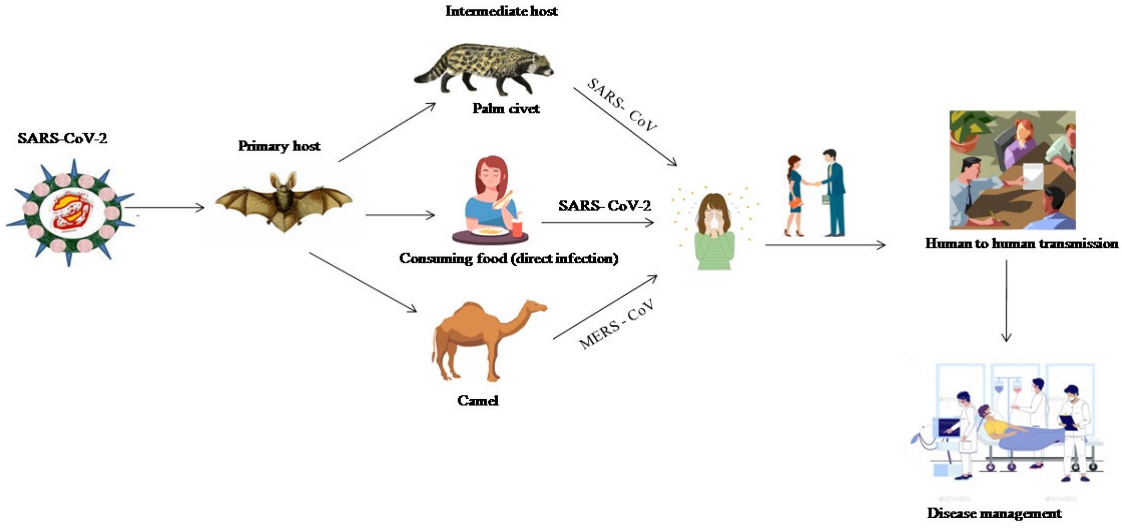

Figure 2. Primary reservoir and mode of transmission of coronavirus

They are considered to have been imparted possibly from bats to humans through some intervening mammalian hosts, known as secondary hosts such as raccoon dogs, palm civets, etc. (Kan et al., 2005; Bolles et al., 2011). An outbreak of SARS was reported in 2002 in China and rhinolophus bats were reported as the key reservoirs (Shiand Hu, 2008). MERS came into existence in 2012 in Saudi Arabia and reported the camel as the zoonotic source (Paden et al., 2018). This virus is transmitted from one person to another via direct contact or cough droplets. The reproduction number [R_o] of coronavirus was reported to be 2-3, which means that, on average, each infected person spreads the infection to an additional two to three persons, and this chain goes on (Liu et al., 2020). It mainly targets the epithelial cells of the lungs. The spike proteins present on the virus's surface attach to the ACE 2 receptors found in the lungs, heart, kidneys, and gastrointestinal tract, thus facilitating viral entry into target cells (Rabi et al., 2020). In a case study, nine COVID-19 positive pregnant women were included that underwent cesarean sections to evaluate the clinical peculiarities of COVID-19 in pregnancy and intrauterine vertical transmission. Amniotic fluid, cord blood, and neonatal throat swab samples were analyzed for the SARS-CoV-2 in the case of intrauterine transmission. The intrauterine transmission was not evident, but clinical presentations in the pregnant women were the same as that of infected adults (Chen et al., 2020).

The Newly Emerged Mutated Strains of SARS-CoV-2

During the global transmission, the SARS-CoV-2 has been mutated several times, leading to the emergence of a new strain of the virus called "SARS-CoV-2 VUI 202012/01". Since November 2020, a hike has been reported in the number of cases in London, accounting for around 60%. This novel strain has been developed through an array of multiple spike protein mutations, including 14 non-synonymous amino acid [AA] altering mutations, six synonymous non-AA altering mutations, and three deletions. These are double deletion 69-70, deletion 144, the combination of N501Y, A570D, D614G in S protein, P681H, T716I, S982A, and D1118H (ECDC, 2020, December 21). The mutation N501Y is foremost and is located within the receptor-binding domain. It can stimulate the binding of S protein with ACE 2 receptors. It has been reported that this strain binds more tenaciously to the human ACE 2 receptor (CDC, 2020, December 29). Therefore, this strain can rapidly evade the host immune response by increasing binding sites and altering the surface structures recognized by antibodies (Volz et al., 2020). These unprecedented mutations make this variant 40-70% more rapidly transmittable than the other circulating strains of SARS-CoV-2 (Singh et al., 2021). A surge has been observed in the number of cases in South Africa due to the epiphany of another mutated SARS- CoV- 2 strain called 501. V2. It is a matter of concern as the 501.V2 changes the shape of spike protein for better binding to the host cells, consequently rendering more contagious infection (Porterfield, 2021). This strain has shown two different mutations i.e., E484K and K417N (Ellyatt, 2021). Lately, scientists at Ohio State University have identified a new strain identical to the UK and South African strain. The variant is named COH.20G/501Y and is highly prevalent in Columbus. It has resulted from three mutations and is highly contagious (Wexner Medical Center, 2021).

Clinical Presentation and Diagnosis of the Disease

The spectrum of COVID-19 presentations varies from mild flu-like symptoms to life-threatening conditions like organ failure. This disease has shown potential comorbidities in young adults, unlike seasonal influenza and pneumonia. The symptoms may emerge 2 to 14 days after the infection. However, Chinese researchers claim the incubation period to be an average of 5.2 days (Li et al., 2020). The most common symptoms reported on the onset of COVID-19 were fever, cough, and fatigue, while other symptoms

include sputum production, dyspnoea, headache, hemoptysis, lymphopenia, and diarrhea (Huang et al., 2020). Older people, kids, and patients having severe health complications like lung diseases, heart diseases, diabetes, and cancer are more vulnerable to the infection as compared to adults. However, some detrimental anomalies may prove to be lethal such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities in subpleural regions of both lungs. In such cases, treatment may not be effective and neurological indications, ischemic and hemorrhagic strokes, and muscle injury may be ascertained (Mao et al., 2020).

The current methods of examination of COVID-19 include detection of the virus by techniques like a polymerase chain reaction or deep sequencing (Guo et al., 2020). Non-contrast chest computed tomography [CT] scans can also be taken into consideration for early diagnosis. Reverse transcription-polymerase chain reaction [RT-PCR] is the standard test for the detection of this virus. However, the efficiency of these methods depends on the presence of viral genome at the site of sample collection. Detection of antibodies, produced promptly after the infection, particularly immunoglobulin M, can be combined with polymerase chain reaction [PCR] to augment detection sensitivity and accuracy. RT-PCR is a genetically engineered in vitro technique used for the detection of the viral genome. Globally, various real-time RT-PCR protocols have been suggested for the diagnosis of COVID-19. These protocols differ in the genes they detect (Chu et al., 2020). However, the core issue with the real-time RT-PCR test is the induction of false-negative and false-positive results. It is stated that many suspected cases with typical clinical characteristics of COVID-19 and similar specific CT images were not diagnosed (Wang et al., 2020). Thus, a negative result does not eliminate the possibility of COVID-19 infection and should not be the only paradigm for treatment or patient management decisions. One of the reports from COVID-19 unveiled a patient with fever, cough, and coarse breathing sounds of both lungs and his sputum showed positive RT-PCR results that confirmed the COVID-19 infection (Lei et al., 2020). The combination of real-time RT-PCR and clinical features aids in managing the SARS-CoV-2 outbreak (Xi et al., 2020). The results from real-time RT-PCR using primers in different genes can be affected by the variation of viral RNA sequences. Gene variation and rapid transformation of this novel coronavirus may result in false-negative results. To avoid false-negative results, multiple target gene amplification can be used.

Another method to detect COVID-19 is a serological test, also called the antibody test. It detects the existence of the virus by identifying the presence of specific proteins on the surface of the virus. Antibody response to SARS-CoV-2 infection usually develops after 7-14 days (Wolfel et al., 2020; Zhao et al., 2020). Lately, serological enzyme-linked immunosorbent assays were designed using recombinant antigens derived from the spike protein of SARS-CoV-2, which encouraged robust and scalable determination of seroconversion. This facilitates the screening of individuals who may experience evidence of past infection (Amanat et al., 2020). Due to an alarming spike in the number of cases every day, proficient testing kits are required.

Prevention and Management of the Disease

Prevention and management of the disease are the two essential tools in the fight against COVID-19. Collaborative measures of public and government are needed to eradicate this disease from its root. Cleanliness and sanitation are essential measures that are highly recommended. Domestic disinfectants may control the growth of the virus on the surfaces. The use of sanitizers and soaps for washing hands is highly recommended. People should wear a mask in public places and should maintain social distancing. Isolation becomes a necessary step as this virus is highly infectious and can spread very fast. Isolation alludes to the segregation of infected individuals from healthy ones. All the suspected patients in the containment

zones are hospitalized and kept in isolation under keen observation until they are tested negative. Patients who are tested positive for COVID-19 are hospitalized until two of their samples are tested negative.

Treatment Options

There is no specific treatment strategy that has shown complete efficacy in the treatment of this calamity but still, some treatment options have been tried that can be used in the management of this disease.

Allopathy

COVID-19 is a highly contagious virus that spreads from person to person. There are not many treatment options for this disease because there are no specific antiviral drugs or vaccines effective against COVID-19 infection.

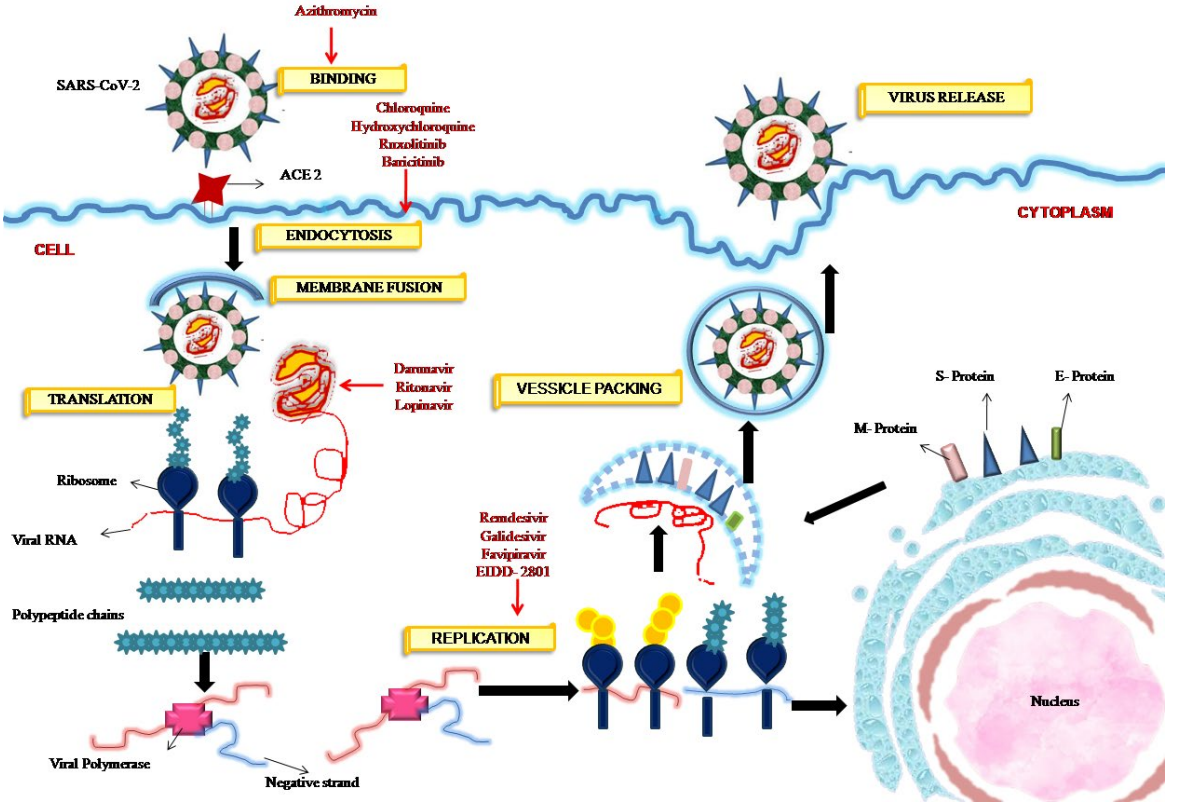

Figure 3. Mechanism of action of various allopathic drugs in the treatment of COVID-19.

One of the approaches to treat this dreadful disease is the use of broad-spectrum antiviral drugs like nucleoside analogs and HIV-protease inhibitors (Lu et al., 2020). The treatment regime that has been used showed that 75 patients were administrated currently available antiviral drugs. The therapy included oral administration of 75 mg Oseltamivir, 500 mg Lopinavir, 500 mg Ritonavir twice a day and the intravenous administration of 0.25 g Ganciclovir for 3–14 days. Previously used drugs in the treatment of SARS-CoV and MERS-CoV, such as a combination of Lopinavir and Ritonavir are also found to be effective (Chu et al., 2004; Momattin et al., 2019). Another report showed that a combination of anti-malarial drugs i.e., Chloroquine and antiviral drug Remdesivir are also effective. Concomitant therapy of Hydrochloroquine and Azithromycin decreased viral burden (Rajaiah et al., 2020). A study conducted at Bichat-Claude Bernard University Hospital, Paris, France, on the compassionate use of Remdesivir in treating COVID-19

reported lucrative results. Complications were reported in patients with advanced disease stages during infusion of Remdesivir (Dubert et al., 2020). EIDD-2801 have shown high therapeutic potential against seasonal viral infections and can be used as another potential drug in the treatment of COVID-19 (Toots et al., 2019). Lately, few patients infected with COVID-19 were treated with combined therapy of 200 mg Lopinavir and 50 mg Ritonavir twice a day and a combination of Oseltamivir and Chloroquine at Sawai Man Singh Hospital, Jaipur, India, and were then tested negative for the COVID-19 infection (Chattopadhyay, 2020). A study reported the effects of Favipiravir vs Lopinavir/ Ritonavir against COVID-19 in a non-randomized clinical trial. In this trial, 35 patients were treated with Favipiravir, and 45 patients were treated with Lopinavir/ Ritonavir for 14 days. It was inferred that Favipiravir was more effective than Lopinavir/ Ritonavir, with a lower incidence of viral load and higher rates of improvement in chest imaging (Cai et al., 2020). The most acceptable way to treat this disease is vaccination. Therefore, vaccines are being processed, and some are at the stage of clinical trials. Recently, a randomized, controlled clinical trial in the United Kingdom has found that a commonly used steroid, Dexamethasone effectively saved the lives of people who were seriously ill with COVID-19. Dexamethasone has been shown to cut deaths by about one-third in patients on ventilators because of coronavirus infection. Immunomodulatory drugs such as Tocilizumab can be used as another management strategy in treating COVID-19 patients with the risk of cytokine storms (Luo et al., 2020). JAK inhibitors like Ruxolitinib and Baricitinib demonstrate both anti-inflammatory and antiviral effects and can be used as a treatment option (Mehta et al., 2020). Figure 3 illustrates the mechanism of action of various allopathic drugs (Ojha et al., 2021).

Unani

Unani medicines or plant-based medicines are non-toxic with lesser side effects. The Unani system is a traditional medicine system that is being explored for providing preventive, supportive, and rehabilitative care to patients. Different plants such as *Glycyrrhiza glabra*, *Allium cepa*, *Allium sativum*, *Curcuma longa, Ocimum sanctum*, *Ocimum tenuiflorum*, *Daucus maritimus*, etc. are effective against viral infections. The decoction of these drugs along with lemon juice and honey was found to be effective against cough and cold (Bano et al., 2013; Fatima et al., 2016; Ghoke et al., 2018; Hashemipour et al., 2014; Konowalchuk and Speirs, 1978; Miladi et al., 2012; Omer et al., 2014; Praditya et al., 2019). An *in vitro* activity of the plant *Glycyrrhiza glabra* was determined and it showed activity against several viruses including SARS-related coronavirus, HIV-1, and respiratory syncytial virus (Fiore et al., 2008). This plant is also effective against various viruses like Influenza A virus [IAV], Human immune virus [HIV], and SARS-associated coronavirus (Anagha et al., 2014). On January 29, 2020, the Government of India released a recommendation based on Indian traditional medicine practices Ayurveda, Homeopathy, and Unani, New Delhi. The advisory includes the ways of preventive management and described a list of some Unani medicines.

Homeopathy

Homeopathy is another efficient therapeutic method in the management and treatment of various diseases. Homeopathic treatment is advantageous as medicine has not to wait until the pathology's cause is found, unlike other treatment options. Therefore, the treatment can be immediate and beneficial for the patient (Kalliantas et al., 2020). According to the Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy [AYUSH] ministry of India, homeopathic medicine Arsenicum album-30 can be administered in the fasted state daily for three days as a prophylactic medicine against the infection. It is highly diluted arsenic trioxide and acts as homeopathic prophylaxis. It targets HT29 cells and human macrophages and thus, reduces NF-κB hyperactivity i.e., decreased expression of reporter gene GFP in transfecting HT29 cells and TNF-α release in macrophages (Bellavite,

2015). As it is not clinically documented that Arsenic album-30 medicine is an effective medicine, it has been criticized by many researchers as pseudoscience. In a clinical trial data from Homeopathy Research Institute, Hong Kong represented 18 people in 6 groups with homeopathic medication. Group one had a female of age 62 who was treated with Bryoniaalb 30C. The other groups had age groups from 18 to 49 and were successfully treated with Bryoniaalb 30C, Gelsemium 30C, Arsenicumalb 30C, and Eupatorium perforatum 30C. All these drugs showed promising effects in the treatment of COVID-19 (Haque et al., 2020).

Plasma from convalescent patients

Convalescent plasma [CP] is a provisional approach for treatment until hyperimmune globulin, drug therapies, and vaccines are available. It has been successfully employed during other coronaviruses outbreaks. Therefore, it is established as the first option in the current situation. The treatment with CP is acquired by using extracorporeal therapy. The plasma of the infected patients is transfused with the plasma obtained from the survivors with the prior infection that contains antibodies against the causative agent of the disease. These antibodies provide passive immunity to the patient by identifying and neutralizing the viral entities (Burnouf and Seghatchian, 2014). A study depicted SARS-CoV-2 specific antibody titers ranging between 1.800 and 16.200, and neutralizing antibodies [Nabs] titers between 80 and 480 in the plasma obtained from the recovered patients of COVID-19, which was infused into the infected patient that reduced the viral load (Shen et al., 2020).

Immunity development

Strong immunity is a crucial weapon in the fight against COVID-19. Both innate and adaptive immune systems are triggered by the invasion of SARS-CoV. The expression of interferon type 1 [IFN-1] is inhibited, followed by inhibition of phosphorylation of signal transducer and activator of transcription 1 [STAT-1] (de Wit et al, 2016). The third defensive response is the immune system enervation through excessive and prolonged IFN-1 production by plasmacytoid dendritic cells [pDCs]. This further leads to an entry of neutrophils, inflammatory monocytes, and macrophages which results in inflammation of the lungs (Prompetchara et al, 2020). A high death rate is observed in older people, probably due to weak immunity, which leads to faster progress of COVID-19 (Li et al., 2005). Intake of vitamin C-rich food such as citrus fruits is recommended. Giloy [*Tinosporacordifolia*], Ashwagandha [*Withaniasomnifera*], and Tulsi [*Ocimum sanctum*] are some of the plants which boost up the immunity and can avenge against COVID-19 by hindering the action of protease M^{pro} or $3Cl^{pro}$. The primary chemical constituents of Giloy e.g., Berberine, β-Sitosterol, Coline, Tetrahydropalmatine, and Octacosanol, can be used against SARS-CoV-2. These compounds target the main protease enzyme that is crucial for virus replication (Chowdhury, 2020). Two compounds, namely Withanoside V and Somniferine, can significantly bind to SARS-CoV-2 $M^{pro}$and can inhibit it. Dihydrodieuginol B and Tulsinol A, B, C, D, E, F, G are the main constituents of Tulsi that have potentially inhibit the protease enzyme (Shree et al., 2020). It is also advisable to take zinc and iodine supplements. Therefore, it is essential to boost our immune system, and hence, the use of immune system boosters should be practiced.

Vaccine research and development

The COVID-19 outbreak is a stark reminder of the ongoing challenge of vaccine development. Robust actions are needed in research and development [R&D] of vaccines to eradicate this disease. The spike protein of the SARS-CoV-2 is the primary target of the vaccine because this can produce neutralizing antibodies that can directly block the virus from infecting healthy cells. According to the global COVID-19 vaccine R&D landscape, about 115 vaccine candidates are there. Out of which, 78 are confirmed, and 37 are unconfirmed. Out of 78 approved candidates, 73 are active and are currently at exploratory or preclinical stages. Some of the candidates like mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio, and LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Ge-

no-Immune Medical Institute are at the clinical stage of vaccine development (Thanh et al., 2020).

A striking feature of the vaccine development landscape for COVID-19 is the multiple strategies that have been employed to generate SARS-COV-2 vaccines, including DNA- and RNA-based vaccines, viral vector vaccines, inactivated virus vaccines, live-attenuated virus vaccines, and recombinant protein vaccines. Recently, the Russian government announced that the country has developed and approved the world's first SARS-CoV-2 vaccine. Gamaleya Research Institute of Epidemiology and Microbiology, Moscow developed the vaccine against COVID-19 named Sputnik V. Sputnik V uses adenoviruses like Ad5 and Ad26 viral vector to deliver the gene for the SARS-CoV-2 spike protein. These are administered in two shots, i.e, 'loaded' Ad26 vector is distributed in the first dose, and the 'loaded' Ad5 vector follows in a second dose after 21 days. This double-vector approach of vaccine administration is quite advantageous as the first dose develops antibodies against the Ad26 serotype. The second dose uses an Ad5 serotype as a vector to enhance the immune response of the body (Dobrovidova, 2020).

A similar approach has been used by the University of Oxford and AstraZeneca, but with a different adenovirus vector which is a chimp vector-like ChAdOx. These adenovirus vectors can cause severe infections such as acute respiratory infections, fever, and diarrhea in humans. The primary issue regarding this vaccine is that it has not yet undergone phase III clinical trials. The lack of accurate data about phase I and II trials exacerbates the cynicism about the safety and efficacy of the vaccine (Caddy, 2020). The m-RNA based BNT162b2 was found to be 95% effective. A comparative study, where four vaccines naming Moderna, AstraZeneca/Oxford, Pfizer/BioNtech, and SputnikV were evaluated and compared for their efficacy and safety. The Moderna, AstraZeneca/Oxford, and Pfizer/BioNtech vaccines seemed effective in preventing COVID-19. No evidence for the ability of the Sputnik V vaccine is published yet. All four vaccines were safe with minor side effects such as headache, joint pain, fatigue, and fever (De and Joseph, 2020). Recently, severe anaphylaxis has been reported in patients who have received the Pfizer and Moderna [mRNA vaccine] vaccines. A report stated the mortality of 29 frail aged persons with serious health problems inoculated with the BNT162b2. Common adverse effects like nausea, diarrhea, and fever were observed (Torjesen, 2021). These vaccines, therefore, may lead to severe consequences and are too risky for the elderly. Covaxin is an inactivated vaccine developed by Bharat Biotech. It is found to be effective against the UK variant of SARS-CoV-2 (Sakpal et al., 2021). A list of vaccine candidates approved and vaccines still under development are mentioned in Table 1 and Table 2, respectively (Regulatory affairs professional society, 2021, January 14).

Table 1. List of approved vaccines.

S.No	Candidate	Type of vaccine	Sponsor
1	BNT162b2	mRNA-based vaccine	Pfizer; BioNTech
2	Covaxin	Inactivated vaccine	Bharat Biotech; National Institute of Virology
3	m-RNA-1273	mRNA-based vaccine	Moderna
4	Corona Vac	Inactivated vaccine (formalin with album adjuvant)	Sinovac
5	BBIBP-Cor V	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)
6	EpiVacCorona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology
7	Sputnik V	Non-replicating viral vector	Gamaleya Research Institute, Acellena Contract Drug Research, and Development

Table 2. List of vaccines under clinical trials.

S.No	Candidate	Mechanism	Trial phase	Sponsor
1	AZD1222	Replication-deficient viral vector vaccine	Phase 3	The University of Oxford; AstraZeneca; IQVIA; Serum Institute of India
2	Ad5-nCoV (Convidicea)	Recombinant vaccine	Phase 3	CanSino Biologics
3	JNJ-78436735	Non-replicating viral vector	Phase 3	Johnson&Johnson
4	NVX-CoV2373	Nanoparticle vaccine	Phase 3	Novavax
5	INO-4800	DNA vaccine (plasmid)	Phase 2/3	Inovio Pharmaceuticals
6	Bacillus Calmette Guerin (BCG) vaccine	Live-attenuated vaccine	Phase 2/3	The University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital
7	VIR-7831	Plant-based adjuvant vaccine	Phase 2/3	Medicago; GSK; Dynavax
8	ZyCoV-D	DNA vaccine (plasmid)	Phase 2	Zydus Cadila
9	AG0301-COVID19	DNA vaccine	Phase ½	AnGes, Inc.

Future Perspectives

WHO has declared COVID-19 as a pandemic as it is spreading at a frenetic pace and has affected millions of people globally. Comprehensive measures are needed to repress the outbreak of COVID-19 and to obstruct the person-to-person transmission. To prevent the spread of this disease, social distancing should be practiced. Preventive measures and health care guidelines for the public and health care workers have been reported by WHO to manage this pernicious disease. This virus is rapidly mutating and emerging into a more infectious pathogen. COVID-19 is culminating in a massive transformation in every sector of life. The worst-case scenario is that numerous industries and governments have succumbed to its effects, due to which a multitude of people have lost their livelihoods. In the best-case scenario, this crisis has also presented an opportunity for more flexible and prudent technology use. Also, this pandemic has led to a tremendous patient workload that makes healthcare providers prone to burnout and depression. Therefore, telemedicine has lingered as a cost controlling and high convenience system. Being a pandemic, COVID-19 is not easy to eradicate, so extensive research is mandatory to combat this deadly disease.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTION STATEMENT

The idea of the manuscript (Kaur L., Singh G), supervision (Kaur L., Singh G., Dhawan R.K), literature search (Mahajan A), article writing (Mahajan A., Kaur L), critical review (Kaur A., Kaur L., Mahajan A).

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