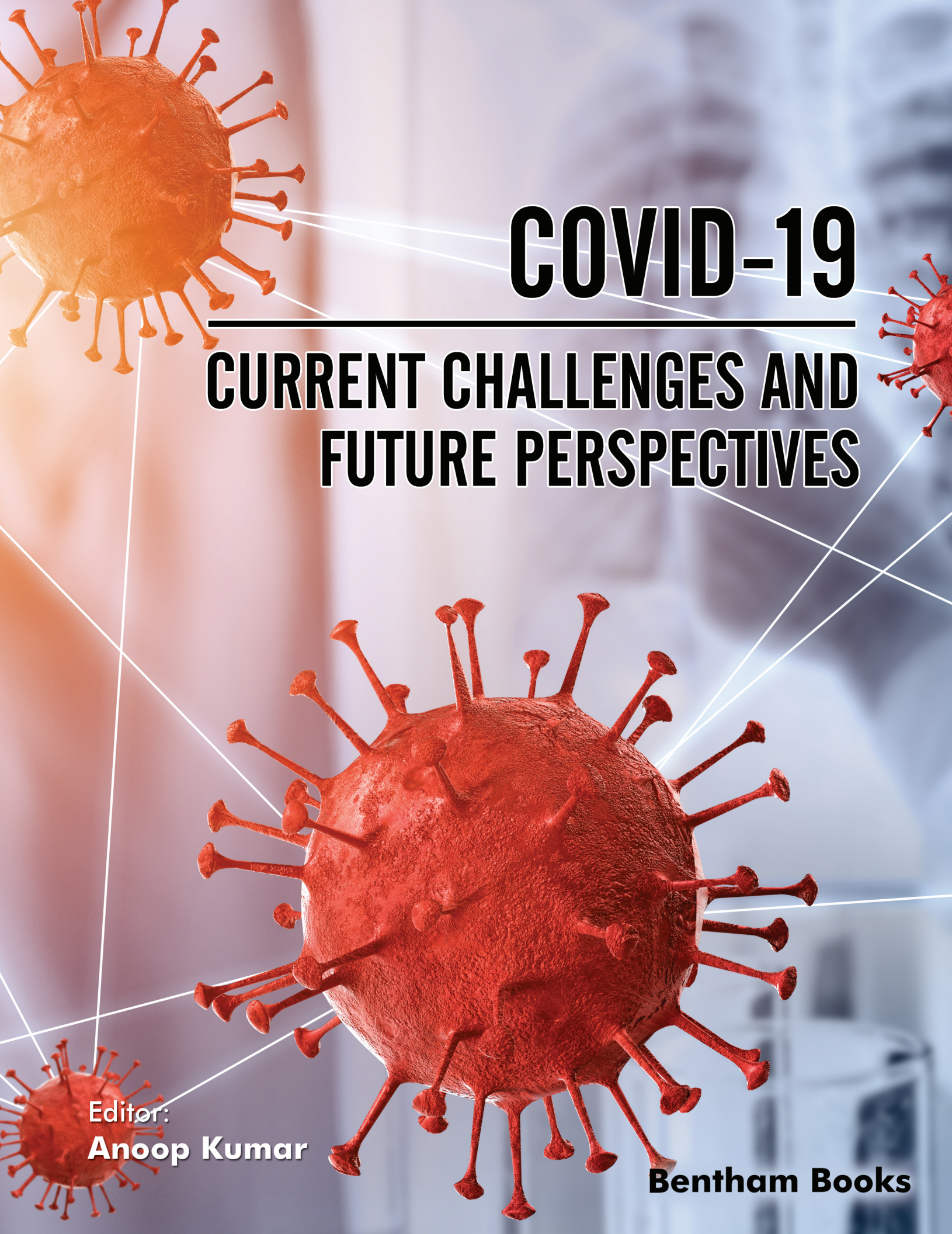

COVID-19

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

Editor:
Anoop Kumar

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COVID-19

Current Challenges and Future Prospective

Edited by

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FOREWORD

Recent novel coronavirus (2019-nCoV) first emerged from China and rapidly spreading all over the world has caused the unprecedented havoc all over the globe. It has been declared a pandemic and global public health emergency by World Health Organization (WHO). The spread of this virus is still continuing despite many drastic containment measures (complete lockdown, curfews, *etc*.). As on 16th June 2020, more than 82,56,725 cases of COVID-19 have been reported over in 190 countries and territories, resulting in approximately 4,45,958 deaths. Health authorities all over the world are struggling to develop possible prevention and therapeutic measure.

This book entitled 'COVID-19:Current Challenges and Future Perspectives' provides a comprehensive view on COVID-19 infection is a guide for health care professionals, researchers, academicians, and regulators. The authors and the publishers need to be complimented for providing timely and useful information.

This book is designed to aid the rapid understanding of the pathogenesis, diagnosis, treatment of COVID-19 infections. I am excited about this book and looking forward to its publication at an early deadline.

S.J.S. Flora
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PREFACE

Recently, a novel coronavirus (2019-nCoV) emerged in China and rapidly spread worldwide. It is declared an ongoing outbreak as a global public health emergency by the World Health Organization (WHO). Currently, health authorities of the world, including India focused on rapid diagnosis and isolation of patients as well as the search for therapies to counter the most severe effects of this infection.

This book intends to bring more rigorous knowledge of COVID-19. This book provides a general introduction about COVID-19, history, diagnosis, treatment, and management, along with its pathological mechanisms. In addition, it also explains the possible mechanism of deaths, targets, repurposing of drugs, herbal medicines in the treatment of COVID-19 infection.

This book has been recognized within 14 chapters presented in a logical sequence. Chapter-1 Introduction. Chapter-2 discusses the History and Epidemiology. Chapter-3 discusses the pathogenesis. Chapter-4 compiled the information regarding diagnostic, treatment, and preventive approaches. Chapter-5 discusses convalescent plasma for treatment of COVID-19 infection. Chapter 6 discusses the effects of early lockdown in India during the outbreak of COVID-19. Chapter-7 provides an overview of COVID-19 altered immune signalling. Chapter-8 discusses about the alteration of brain signalling pathways due to COVID-19. Chapter-9 discusses about the risk factors and complications associated with COVID-19. Chapter-10 provides an overview of the possible mechanism of deaths. Chapter-11 discusses the possible targets. Chapter-12 briefs about the repurposing of drugs. Chapter-13 provides an overview of herbals for COVID-19 infections. Chapter-14 discusses current challenges and future perspectives.

The editor wishes to express their considerable appreciation to the Publisher who took over the management of the production of this book in difficult circumstances and whose contribution is much appreciated. We trust this book will be useful to researchers, students as well as the general public and we believe that better knowledge of this virus could result in the effective treatment.

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CHAPTER 1

Introduction

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China, affecting millions of peoples worldwide, and was declared as a global health emergency by the World Health Organization (WHO). This infection is extremely transmittable from humans to humans due to its long incubation period (as compared to other viruses of the same category), which results in asymptomatic carriers. The complete knowledge regarding this virus is still unclear and various studies are being conducted worldwide. Till now, no vaccines or specific drugs are available for its prevention and treatment. However, various classes of drugs are repurposed for their treatment and many new drugs and vaccines are under development. This chapter provides brief information related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) along with its diagnosis, prevention, and treatment strategies.

Keywords: Biological disaster, Coronaviruses, Humans, Mammals, Respiratory syndrome.

INTRODUCTION

Coronavirus (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. This virus originated from Wuhan city of China and then spread all around the world [1, 2]. The name of this virus is "Corona" which might be due to the presence of crown-like projections on the outer surface and in Latin, "Corona" means "halo" or "crown [1, 3, 4]". The Coronavirinae and Torovirinae are the two subfamilies of the Coronavirinae. Further, the family of Coronavirinae is divided into four genera *i.e.* alpha (α), beta (β), gamma (γ), and delta (δ) coronaviruses [5 - 7]. As per the phylogenetic studies, a set of viruses is arranged into these genera [7, 8].

Past decades witnessed only two human coronaviruses (HCoV-229E and HCoV-OC43). However, later on, in 2002, four new human coronaviruses were identi-

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fied [9 - 11]. In 1931, the first disease caused due to corona was identified, but the isolation of coronavirus (HCoV-229E) from humans was done in 1965 [12, 13]. Only two human coronaviruses (HCoV) *i.e.*, HCoV-229E and HCoV-OC43, were identified till a big burst of severe acute respiratory syndrome virus (SARS-CoV) happened in the year 2002 [14, 15]. Further, four human coronaviruses were identified, including new COVID-19 after the discovery of severe acute respiratory syndrome virus (SARS-CoV) [15 - 18]. The detailed history of coronaviruses is provided in Chapter 2. The pathogen interacts with humans in many ways and various factors play a major role in the rapid spread of a particular infection throughout a population or community. This chapter provides brief information about the newly emerged coronavirus along with the available treatment options.

STRUCTURE

Coronaviruses are enveloped, spherical, and positive sense (+), single-stranded RNA virus [17 - 22]. The virus enters the host and releases messenger RNA (mRNA), which initiates the synthesis of RNA, leads to replication and transcription, and further packages into the progeny virus [19, 23]. The spike protein (S), membrane protein (M), an envelope protein (E), and nucleocapsid protein (N) are structural proteins of this virus [24 - 27]. Nucleocapsid protein (N) is an RNA-binding protein that contains N-terminal and a C-terminal domain [26], whereas spike protein (S) is a glycoprotein that helps in the attachment of the virus with the host. The spike glycoprotein is cleaved into S1 and S2 (two different polypeptides) by host cell proteases [26, 28]. The membrane protein (~25–30 kDa) is composed of three types of domains that provide the shape to the virion membrane [26, 29]. The protein which is present on the complete surface of the coronavirus is envelope protein (E) (~8–12 kDa), composed of N-terminal ectodomain and a C-terminal endodomain, which plays an important role in ion channel activity [26, 30]. Apart from these four structural proteins, there is another protein known as hemagglutinin-esterase (HE), which exists in a few beta coronaviruses [26, 31]. This protein helps in the binding of sialic acids on surface glycoproteins and contains acetyl-esterase activity [26, 32, 33]. The various proteins of coronavirus are shown in Fig. (**1**).

TYPES

Coronaviruses are categorized into two major types *i.e.*, animal and human coronaviruses, which are discussed below:

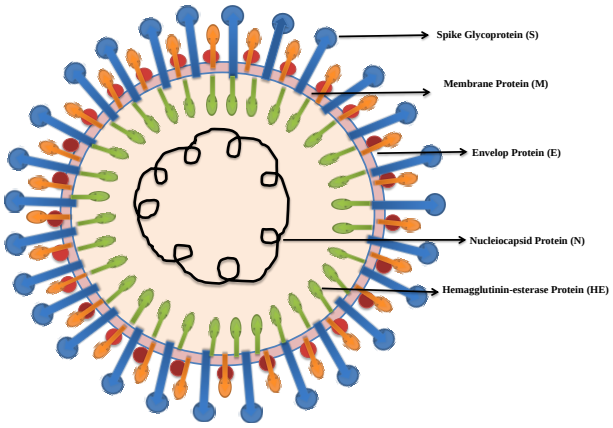

Fig. (1). Structure of coronavirus.

Animal Coronaviruses

The coronaviruses cause severe acute respiratory syndrome (SARS), thought to emerge from animals [34]. These viruses result in severe diseases in animals and researchers started to work on these viruses at the start of the 20th century [35]. The researchers have identified the porcine epidemic diarrhea CoV (PEDV) and Transmissible Gastroenteritis Virus (TGEV) to cause severe gastroenteritis, which results in the deaths of baby pigs [36]. The corona-viruses have been identified in bats in the last couple of decades, which are likely to have induced severe acute respiratory syndrome [37].

Human Coronaviruses

Prior to the COVID-19 outbreak, two alpha coronaviruses (HCoV-229E and HCoV-NL63) and two beta coronaviruses (HCoV-OC43 and HCoV-HKU1) were known. Emerging reports have indicated a close relation of SARS-CoV-2 with bat coronavirus [38, 39]. The coronavirus infection results in approximately 15–30% of respiratory infections in humans every year. The frequency of infections is found to be increased in neonates, the elderly, and individuals with underlying illnesses. The beta coronavirus SARS-CoV was identified in 2002-2003 in the Guangdong Province of China [40 - 42] and spread to many countries. Approximately 774 deaths were recorded in 8098 infected cases. The mortality was observed specifically in the elderly and individuals with underlying illnesses [43]. Recently, SARS-CoV-2 was identified and its actual source is likely to be bats (not confirmed yet).

GLOBAL IMPACT

SARS-CoV-2 infection has affected the world in a big way (CDC, 2020). The regulatory authorities of the World are continuously monitoring the effect of this

CHAPTER 2

History and Epidemiology of COVID-19

Ruchika Sharma*

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Abstract: Researchers identified human coronaviruses (HCoV), for the first time in the year 1960s, to be responsible for cold. However, later that decade, it was observed that these viruses also affect the upper and lower respiratory tract and are probable common human pathogens. The last few eras witnessed the emergence of novel zoonotic viruses, including recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19). The COVID-19 disease is extremely infectious and transmittable, which results in severe acute respiratory syndrome. This virus emerged in China's Wuhan city wet market and spread globally within a few months. Molecular data analysis of genome revealed similarity of SARS-CoV-2 with severe acute respiratory syndrome-like (SARS-like) bat viruses. The evidence for zoonotic virus spillover is not known, whereas the virus passes from human to human rapidly. This chapter discusses the origin of human coronaviruses and their distribution. Further, the global epidemiology of COVID- 19 is also discussed.

Keywords: Biological disasters, Coronavirus, Epidemics, Human pathogens, Pandemics, Respiratory syndrome, Spillover, Viruses, Zoonotic.

INTRODUCTION

Globally, throughout human history, several different microbial contagious agents have been responsible for biological disasters [1]. History is replete with different instances of exactly how these disastrous biological outbreaks resulted in epidemics and pandemics [1, 2]. These types of threats still affect societies globally. Most of the time, these disastrous outbreaks are natural and accidental, but sometimes biological disasters may also be intentional. These natural biological threats result in epidemics and pandemics, further leading to substantial morbidity and mortality. Many factors are responsible for a particular infection and rapid spread into the population (Fig. **1**). Enormous factors (genetic and biological) contribute to the emergence of an infectious disease [3, 4]. When a virus passes from animals to humans, it is called a zoonotic virus and a first-time transmission event is called spillover.

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Anoop Kumar (Ed.)

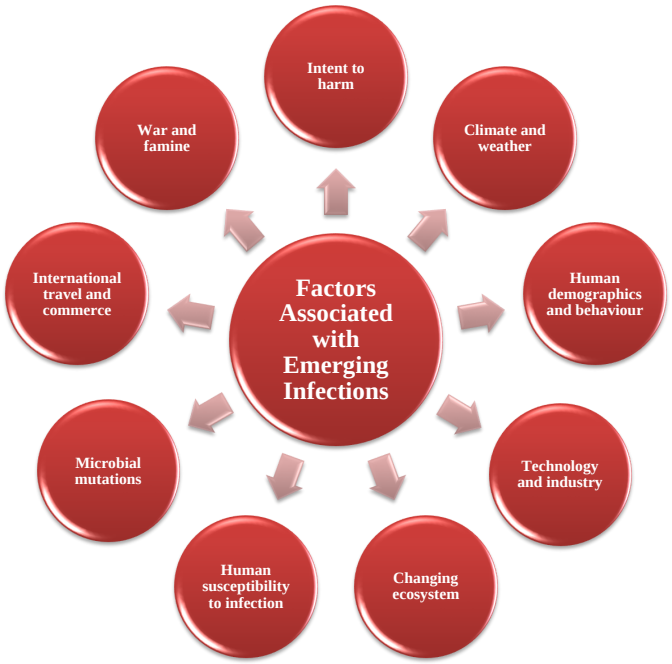

Fig. (1). Factors associated with emerging infections.

CLASSIFICATION

"Corona" in Latin means "halo" or "crown." Coronaviruses possess a distinctive morphology; the name comes from the outer surface crown-like projection (crown of embedded envelope protein) of the virus [5]. International Committee for Taxonomy of Viruses (ICTV) classified coronaviruses (CoVs) as a principal group of viruses that fall into the Nidovirales order and Coronaviridae family. The Coronaviridae family comprises two subfamilies *i.e.* Coronavirinae, and Torovirinae (Fig. **2**). Further, the coronavirinae subfamily is divided into four genera, alpha (α), beta (β), gamma (γ), and delta (δ) coronaviruses [6, 7].

Additionally, a set of viruses are arranged into these genera based upon the phylogenetic studies (Table **1**). The seven species of coronaviruses have been identified that infect humans [3]. Four are endemic (regularly found in certain areas and seasons) and cause mild infection, whereas three cause severe symptoms, which are sometimes fatal [4].

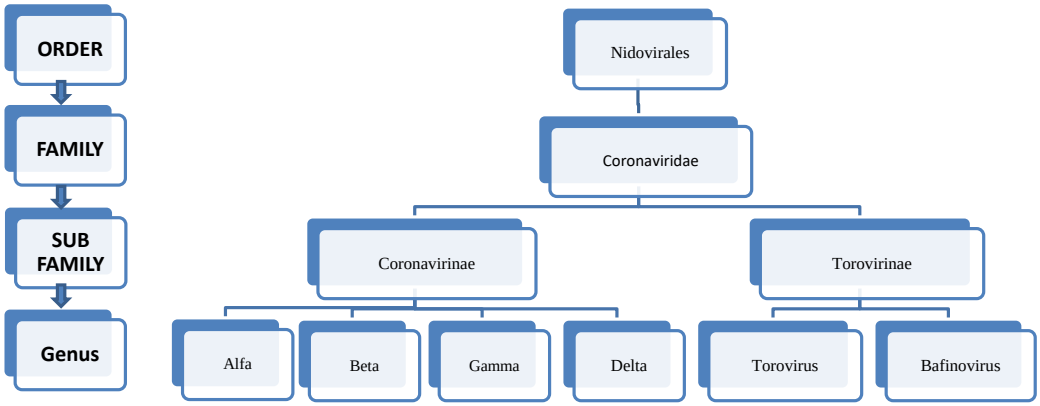

Fig. (2). Classification of coronavirus.

Table 1. Names of coronavirus and their respective host.

Genus	Species Name	Host
Alfa	Human coronavirus 229E (HCoV-229E)	Bat
	Human coronavirus NL63 (HCoV-NL63)	Bat, Palm civets
Beta	Human coronavirus OC43 (HCoV-OC43)	Cattle
	Severe acute respiratory syndrome coronavirus (SARS-CoV)	Palm civets
	Human coronavirus HKU1 (HCoV-HKU1)	Mice
	Middle East respiratory syndrome-related coronavirus (MERS-CoV)	Bat, Camels
	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19)	Possibly (Bat)

Strains of human coronaviruses that cause mild cold symptoms mostly in winters and early springs are coronavirus OC43, NL63, HKU1, 229E. Two strains, OC43 and 229E, have been found responsible for 10-30% of all common colds since the 1960s [6, 7]. However, these strains cause severe infection when co-infection occurs with other viruses or bacteria present in the body whereas, the rest of the three strains cause severe conditions called deadlier strains, which are severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus, and Severe acute respiratory syndrome coronavirus 2.

According to the International Committee for Taxonomy of Viruses, alpha and beta coronaviruses both infect only mammals whereas, gamma and delta coronavirus infect birds, and sometimes mammals (Fig. **3**) [7].

CHAPTER 3

Pathogenesis of COVID-19

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Abstract: The pathogenesis of coronavirus 2019 (COVID-19) disease is unclear so far. However, emerging reports have revealed how this virus enters the body and affects various organs and finally results in the death of the patients. This chapter mainly compiled the information related to the pathogenesis of COVID-19 infection.

Keywords: Case reports, Clinical manifestations, COVID 19, Pathogenesis, Viral entry.

INTRODUCTION

Novel coronavirus (nCoV) is one of the most serious causes of respiratory illness, atypical pneumonia that was first identified in November-December 2019 in Wuhan, China. This recently discovered coronavirus belongs to the group of beta coronaviruses [1]. This group also includes other viruses such as severe acute respiratory syndrome virus (SARS-CoV) and middle east respiratory syndrome-related coronavirus (MERS-CoV) [2]. These viruses mainly target the respiratory system of humans due to which symptoms like other flu such as cough, fever, breathing problems, diarrhoea, gastrointestinal disturbances, *etc.* are observed. The viral transmission occurs through coughing or sneezing of the infected person and consequences may result in severe respiratory distress and pneumonia, which can even lead to death [3]. According to the World health organization (WHO), from December 2019 to March 2020, there were approximately 7,86,228 reported cases, out of which 37,820 patients had died [4]. The patient's mortality rate was observed to be high, particularly in elderly patients and patients suffering from co-morbid conditions like hypertension, cardiovascular disease, diabetes or other respiratory problems [2]. Still, there is no complete information regarding corona-

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virus disease 2019 (COVID-2019) and there are many questions, which need to be answered regarding pathogenicity, treatment, challenges, transmission, *etc*. [5]. This chapter compiled information particularly related to the pathophysiological mechanism of COVID-19 infection.

PATHOGENESIS

Life Cycle of a Virus

The nCoV is mainly zoonotic as that of SARS-CoV, MERS-CoV and probably transmitted from animals to humans. The recent literature has reported that the nCoV might have spread from the local seafood market of Wuhan, China [3]. However, the exact source is still not confirmed. The human to human transmission occurs through respiratory secretions such as droplets, fecal-oral route, virus-contaminated surfaces, and being close to the infected persons.

Entry and Replication of the Virus Inside the Host

The genome of the novel coronavirus is a single positive-strand RNA virus, which belongs to the *Coronaviridae* family. The genome encodes an open reading frame (ORF), which contains structural and non-structural proteins (Fig. **1**).

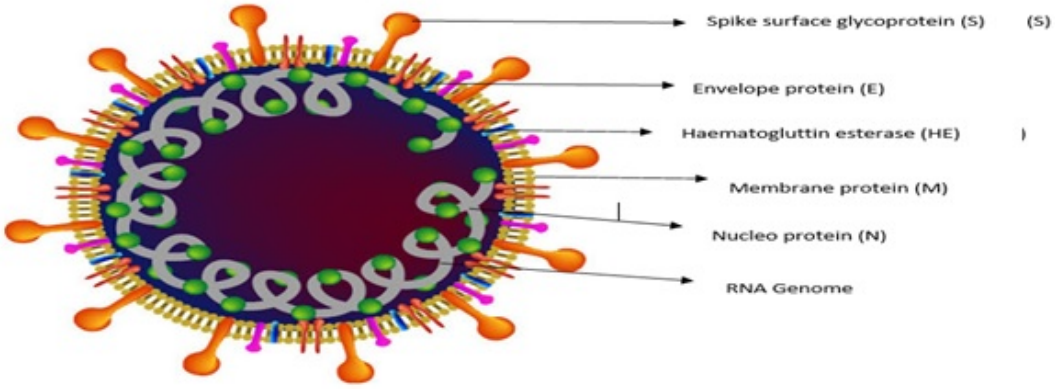

Fig. (1). Novel coronavirus structure.

The structural proteins include small enveloped protein (E protein), spike surface glycoprotein (S), nucleocapsid protein (N), and matrix protein (M), whereas seven non-structural proteins are also present [6]. The surface of coronavirus contains spike surface glycoprotein that intermediates attachment to the host receptor. The glycoprotein consists of N-acetyl neuraminic acid (NAG) that supports the connection of virus to cell surface receptors *i.e.* angiotensin-converting enzyme 2

receptor (ACE 2), followed by fusion of viral membrane to the host cell membrane. Mostly, coronavirus spike glycoprotein split into separate polypeptides known as S1 and S2 through a host cell protease and genome released into the host [8]. Later, the genome replication begins; the RNA polymerase presents in the viral genome helps in replication, which encodes positive and negative-stranded RNA. Further, positive-stranded RNA encodes two large ORFs, which serve as polyproteins. These polyproteins subsequently cleave into non-structural proteins. The genome also encodes protease NS3 protein. Subsequently, the negative-stranded RNA is transcribed into small positive-stranded RNA, which further replicates into a new virus. On the other hand, all the prepared proteins bind to RNA and are fused into the endoplasmic reticulum of humans. Formerly, the membrane protein of coronavirus assists all the proteins in getting a viral assembly. Further, all non-structural proteins are assembled and virus progeny releases outside of cell through exocytosis [9] (Fig. **2**).

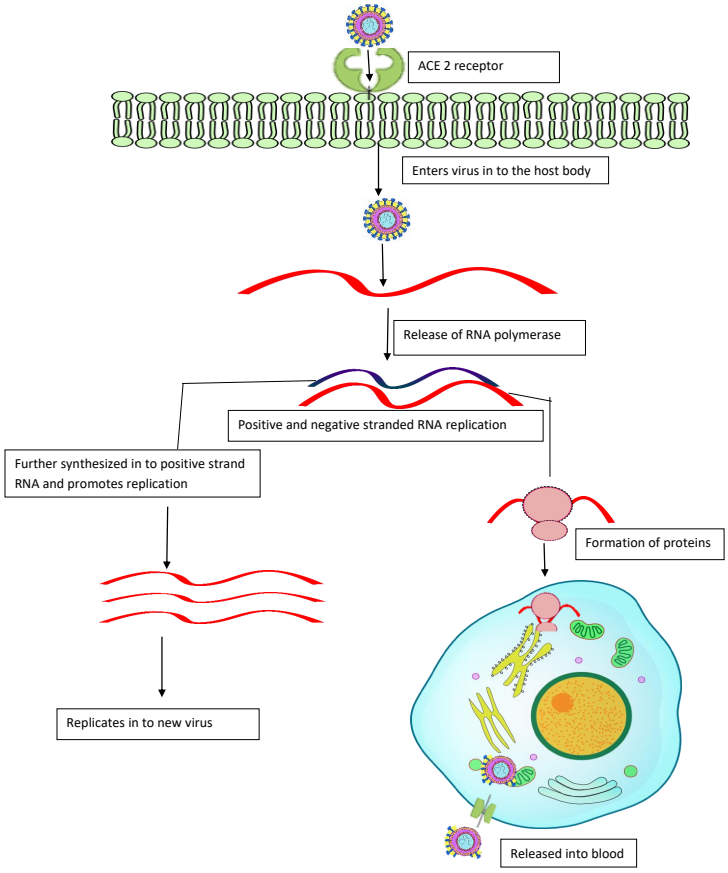

Fig. (2). Entry of virus into human and replication of virus.

CHAPTER 4

Diagnosis, Treatment and Management of COVID-19

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Abstract: Currently, reverse transcription-Polymerase chain reaction (RT-PCR) and real-time reverse transcription-polymerase chain reaction (rRT-PCR) are used for the diagnosis of COVID-19 patients. COVID-19 antibodies can be reliably detected only around 15 days after disease onset, whereas; rRT-PCR allows the detection of virus within the first week of illness. The various diagnostic tests are under development. The treatment of the patient depends upon the individual case. Currently, no specific drug or vaccine is available for its treatment. Symptomatic treatment is the only option. This chapter brings into notice the diagnosis, management, and treatment methods used so far for COVID-19.

Keywords: COVID-19, Polymerase chain reaction (PCR), SARS-CoV-2, Treatment and Management.

INTRODUCTION

In the capital of Hubei (Wuhan), news spread about the occurrence of a novel pneumonia-like illness in December 2019. After the investigations, it was reported that this pneumonia-like illness is caused by a virus called a novel coronavirus. After a while, in February 2020, WHO decided to name it as the novel coronavirus disease 2019 (COVID-19), and later on, it was known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). In its initial stages, the infection expanded very rapidly throughout the world. Globally, the

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total number of 860,927 confirmed cases were reported with 42,364 deaths till 1 April 2020 [1].

Currently, reverse transcription-PCR (RT-PCR) and real-time reverse transcription-polymerase chain reaction (rRT-PCR) is being used for the diagnosis of patients. The early diagnosis and management of the patients will be helpful in controlling the spread of this infection. However, diagnosis of COVID-19 infection, particularly based on symptoms, is a challenging task as it overlaps with other flu symptoms [2]. This chapter mainly focuses on the diagnosis, treatment, and management of COVID-19 patients.

DIAGNOSTIC APPROACHES

Currently, various methods are being used to diagnose the COVID-19 infection, such as physical symptoms, specific laboratory tests, imaging techniques, *etc.*, which are discussed below in detail.

Physical Symptoms

Numerous symptoms have appeared in infected persons, but symptoms may vary in infected individuals. The fever is most common that is why thermal scanning is most commonly used for screening. However, fever is not a must in all infected individuals. The other most common symptoms observed are dry cough, tiredness, muscle ache, conjunctivitis, headache, sore throat, rhinorrhea, chest pain, shortness of breath, loss of taste or smell, nausea, and vomiting. In some individuals, diarrhoea, renal function tests, acute cardiac injury, deranged liver, multiorgan dysfunction syndrome, lymphopenia, multi-organ failure, and septic shock are also observed. Headache, confusion, and delirium experienced by some COVID19 patients could be the result of the coronavirus directly invading the brain.

Laboratory Tests: Sample Intake Methods, Analysis

Molecular Tests (Antigen)

According to WHO, the specimens should be collected from nasal and oropharyngeal routes (the upper respiratory tract) and the broncho alveolar lavage (BAL), and expectorated sputum (lower respiratory tract). It is suggested that the BAL specimens should be taken in the case of mechanically ventilated patients, and it was found that it remains positive for an extended duration. The samples should be stored at 4 degrees Celsius [3]. These samples are diagnosed by a very popular method known as reverse polymerase chain reaction (RT-PCR), which works on the principle of the synthesis of complementary double-stranded DNA

(cDNA) from RNA [4]. The probe was used according to the initial gene sequence given by the Shanghai Public Health Clinical Centre and School of Public Health, Fudan University, Shanghai, China, on Virological.org [5]. The diagnostic test should be repeated on a regular interval for vial clearance if the test is found positive [6].

The cycle threshold or Ct value of an RT-PCR reaction is the number of cycles at which fluorescence of the PCR product is detectable over and above the background signal. Theoretically, the Ct value is inversely proportional to the amount of genetic material (RNA) in the starting sample and lower Ct values generally correlate with high viral load.

The pooled samples are useful to screen a large number of populations at a faster rate. The pooling samples involve mixing several samples in a "batch", then testing the pooled sample with a diagnostic test. The number of samples may be tested together, using only the resources needed for a single test. However, because samples are diluted, which could result in less viral genetic material available to detect, there is a greater likelihood of false-negative results, particularly if not properly validated.

Serology

In the first 2 weeks of the infection, it is not recommended to go for an antibody test. The detection of anti-SARS-CoV-2 antibodies may be useful for confirming the presence of current or past infection in a selected situation. If we are treating a patient for 2 weeks and his/her RT PCR test is negative, but symptoms are related to COVID-19, in that case, if the patient would like to know whether he/she was COVID-19 positive or not, an anti-body test (IgG) can be done. If the antibody is formed, that means he/she was COVID positive. The most appropriate time to do this test is around 21-28 days after the infection. It has been observed that all the infected persons will not always have antibodies. Research is ongoing to develop a specific serological test for the diagnosis of COVID-19 by the US Vaccine Research Centre at the National Institutes of Health [7].

Hematological Examination

The complete hematological profile could provide an idea regarding the severity of the COVID-19 patient. The total white blood cell count (WBC) was found normal and decreased in the initial stage of COVID-19 infection. However, the level of muscle enzymes, liver enzymes, and lactate dehydrogenase (LDH) was found to be increased. The erythrocyte sedimentation rate (ESR), IL-6 level, C-reactive protein (CRP) and eosinophil level will provide a clear idea about inflammation in the individual. The procalcitonin value was detected to be normal

CHAPTER 5

Convalescent Plasma for Treatment of COVID-19 Infection

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Abstract: In the beginning of the 21st century, many viral infections were reported with a significant impact on the socio-economic growth of many nations globally. Many new strains of viruses were reported in the recent past. Passive antibody therapy involves antibody administration against various viruses. Though vaccines are available for many diseases, however, a longer duration is required for the development of a vaccine for novel viruses like the COVID-19 outbreak. In such cases, passive antibody therapy plays a major role in providing instantaneous immunity to susceptible persons. Proofs predicted that patients receiving convalescent plasma recovered from the disease and utilized it as a treatment without any serious antagonistic occasions. In this manner, it may be beneficial to test the safety and adequacy of convalescent plasma transfusion in SARS-CoV-2 contaminated patients. In this chapter, the authors conducted a brief literature review on treatment options against novel coronavirus. This chapter emphasized on the use of plasma therapy against novel Coronavirus and its future perspectives.

Keywords: Antibodies, Antiviral, Convalescent plasma therapy, Coronavirus, mAb, Remdesivir.

INTRODUCTION

The past few decades witness many novel strains of viruses, which have had a great impact on socio-economic growth throughout the world. Recently, the end of 2019 reported the emergence of a new strain of virus from the family of *Coronviridae* and has brought the world's economy at a stand-still, affecting the lifestyle of people across the globe. Coronavirus belongs to the largest family of viruses, called the *Coronaviridae* family belonging to the nidovirales order [1 - 6].

The outbreak of coronavirus 2 (SARS-CoV-2), with its epicenter in Wuhan, China transmitted across the globe. Pneumonia due to the SARS-CoV-2 is known as

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Coronavirus ailment 2019 (COVID-19). Despite supportive care, like oxygen source in case of mild suffering and extracorporeal film oxygenation for seriously sick individuals, explicit medications for this sickness are under investigation. In the USA, principal treatment is provided with steady consideration and intravenous (IV) administration of remdesivir. However, randomized clinical trials assess the adequacy of remdesivir in the treatment of COVID-19. Convalescent-based plasma therapy or immunoglobulins are administered to patients if all the above treatments failed to improve the survival of patients suffering from SARS. Also, a few investigations demonstrated a shorter emergency with a low rate of mortality in patients treated with convalescent plasma in comparison to individuals not treated with convalescent plasma. In 2014, the utilization of convalescent plasma gathered from patients who recouped from the Ebola infection problem was suggested by WHO as an observational treatment during outbursts [7]. Moreover, in a subgroup examination, after receiving convalescent plasma therapy, the viral burden essentially decreased on 3rd, 5th and 7th day. Hung *et al.*, and co-workers [8] performed a prospective, multicentre, double-blind randomized controlled trial by using convalescent plasma therapy. The plasma of patients recovered from influenza A H1N1pdm09 was used to treat patients suffering from extreme influenza A H1N1 infection, and patients were observed with a lower viral burden as well as diminished mortality within 5 days of treatment. A meta-investigation by Mair-Jenkins and associates [9] demonstrated that the mortality rate was decreased in the wake of different dosages of plasma therapy to patients suffering from severe acute respiratory infections and no adverse events were reported after the treatment. In another meta-investigations by Luke *et al.*, and co-workers [10], conducted 8 studies and identified the involvement of 1703 patients who received an infusion of antibody against influenza in the form of plasma, which showed 21% reduction (95% Cl 15-27; $p<0.001$) in overall fatality rate at low risk. Schoofs *et al.*, and associates [11] had reported 3BNC117-mediated immunotherapy, which neutralized antibodies to HIV-1, and improved host humoral immunity to HIV-1. *In vivo* trial indicates that the impact of antibodies was not limited to free viral removal and inhibition of new contamination and increases the clearance of infected cells. The patients normally build up primary immune response by 10-14 days, which is trailed by infection clearance. Therefore, hypothetically, it ought to be more effective to administer the convalescent plasma at the initial phase of the disease. According to WHO, the board of COVID-19 is predominantly centred around contamination anticipation, case identification, checking and strong consideration. However, no particular anti-SARS-CoV-2 medication is suggested due to the nonexistence of proof. Most importantly, the present rules accentuate that systematic corticosteroids ought not to be given routinely for the treatment of COVID-19, which was an additional suggestion in the Lancet. Proof predicted

convalescent plasma of patients who have recovered from the disease can be utilized as a treatment without the serious antagonistic event. In this manner, it may be beneficial to test the safety and adequacy of convalescent plasma transfusion in SARS-CoV-2 contaminated patients. In this book chapter, the authors discussed a brief literature review of treatment options against novel coronavirus. This chapter emphasized the use of plasma therapy against novel coronavirus and its future perspectives [12 - 16].

TREATMENT OPTIONS EXPLORED TILL DATE

COVID-19 transmission from person to person led to patient isolation [17]. Presently, till date, there is no specific therapy available that proves to be accurate against COVID-19 infection [18 - 20]. Till date, patients are monitored with broad-spectrum antiviral drugs belonging to various classes like anti-HIV protease inhibitors, nucleoside analogues, which work for the attenuation of viral load in plasma [21]. As time passes and clinical trials are undertaken by various regulatory agencies to determine which dosage regimen fits best for combating the COVID-19 infection in humans. With the advancement of days, new dosage regimens are being created and old dosage regimen being modified. The dosage regimen which is followed, includes oral administration of oseltamivir 75 mg twice a day, ritonavir 500 mg, ganciclovir 0.25g administered *via* I.V. route and continued for 3-14 days depending upon patient condition [6]. Some reports of administration of remdesivir broad-spectrum antiviral in combination with chloroquine proved to be highly effective for managing Coronavirus infection in *In-vitro* studies [22 - 24]. Administration of these antiviral compounds to human patients had proved to be safer and efficacious. According to recent reports, >85% of patients receive antiviral agents, including oseltamivir and lopinavir/ritonavir tablets and ganciclovir. Prescription of empirical antibiotics is given to near 90% of patients [25]. Clinical data and various studies claimed the IV administration of immunoglobulin as well as systemic steroids, but their efficacy as well as associated adverse effects, remains unclear [26 - 30].

Historical Background of Passive Antibody Therapy

Passive antibody therapy was discovered in the early 1890s by Behring and Kitasato. This therapy is mainly used to treat infectious diseases. All antibody preparations were obtained from immunized animals and immune human donors. This therapy is also known as serum therapy. This therapy has some side effects, but it has overcome antibody purification methods in the 1930s, which results in reduced toxicity, but in 1935, the antibody therapy declined rapidly due to the introduction of sulphonamide antimicrobial therapy. In the 1940s, serum was largely abandoned as an antibacterial agent due to the introduction of β-lactam

CHAPTER 6

Effect of Early Lockdown in India During the Outbreak of COVID-19: A Comparative Study of USA, Italy and India

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Abstract: Recently, the World Health Organization (WHO) has declared COVID-19 as a worldwide public health emergency. The mode of transmission of COVID-19 appears to be from humans to humans. There is no vaccine or specific drug available for its treatment. To reduce the spread of this disease, reduction of the human to human contact is required. Therefore, the concept of social distancing and community lockdown prevails as one of the preventive measures. Some of the countries followed early community lockdown, while some adopted it at a later stage. The community lockdown could be effective in reducing the spread of COVID-19. However, management of the same still remains a matter of concern.

In the present study, we have extracted data from WHO daily situation reports and have compared the disease progression per week from the first identified confirmed case of USA, Italy and India. Our observation indicates that the number of cases in India is significantly lesser as compared to the USA and Italy. This might have happened due to the early lockdown in India.

Keywords: COVID-19, Early Quarantine, India, Italy, Lockdown, Social isolation, USA.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or novel coronavirus (nCov) induces pneumonia disease which is termed as coronavirus disease 2019 (COVID-19), which majorly affects the human respiratory system.

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The prime suspect of the disease has been observed in Wuhan, China, in December 2019. Recently, the World Health Organization (WHO) announced COVID-19 as a global public health emergency [1]. The COVID-19 has spread rapidly across the countries affecting around 212 countries around the world [2]. Previous outbreaks of coronaviruses (CoV) include the Severe Acute Respiratory Syndrome (SARS-CoV) and the Middle East Respiratory Syndrome (MERS-CoV) [3].

The symptoms of COVID-19 include fever, dry cough, and headache, myalgia, and fatigue, which appear similar to flu-like symptoms and make it difficult to diagnose. Around 13-14% cases suffer from pneumonia and dyspnea whereas, 5-6% of cases appear to be associated with severe respiratory failure and/or multi-organ failure [4]. While asymptomatic cases are also reported *i.e.* of the 634 confirmed COVID-19 cases on board, the Diamond Princess Cruise ship, Yokohama, Japan and a total of 328 and 306 were reported to be asymptomatic and symptomatic, respectively [5]. Another study, which estimated the asymptomatic ratio by using information on Japanese nationals that evacuated from Wuhan, China on chartered flights, showed that among 565 evacuees, the asymptomatic ratio was found to be 41.6% (95% confidence interval (CI): 16.7%, 66.7%). These evidence suggest that nearly half of the victims of COVID-19 are asymptomatic [6]. The highly contagious nature of SAR-CoV-2 is probably due to asymptomatic spread [7].

COVID-19 is a novel virus, nobody has prior immunity to it and thus, the entire human race is prone to infection. It appears highly contagious in humans and primarily spread through respiratory droplets *via* cough or sneeze. The major mode of transmission appears to be inhalation of droplets and contact with infected surfaces. In humans, angiotensin-converting enzyme 2 (ACE2) facilitates the attachment of the spike protein of COVID-19 and its invasion to host cells. The other protein which helps in the virus entry is the trans-membrane protease serine 2 (TMPRSS2) through spike priming [8].

Most of the mortality in SARS-CoV-2 infection is due to the acute respiratory distress syndrome, which occurs due to the over activation of cytokines (cytokine storm) in the lungs [9]. Apart from it, acute kidney damage [10], cardiovascular complications [11] and some cases of liver damage have also been reported [9].

Despite this pandemic situation, effective treatments and vaccines are still under development. At present, symptomatic treatment appears as a putative strategy to improve patient health care. WHO and national reports consistently indicated that quarantine and lockdown are important in reducing the number of positive cases and the number of deaths during the COVID-19 pandemic condition [12].

Quarantine duration of 14 days (estimated incubation period of SARS-CoV-2) was recommended by WHO and by the US Center for Disease Control and Prevention for the individuals who were in direct contact with the confirmed case or having the travel history from the countries with the declared outbreak. To control the rapid spread of COVID-19, the use of suitable facemasks, alcohol-based sanitizers, social isolation, self-quarantine, social distancing, travel restrictions, and community lockdown appear effective in restricting the spread of infection and considered as the suitable way to respond to this pandemic situation [13].

Despite several preventive measures, the progression of the disease is on the rise exponentially. The first case in the USA, Italy, and India was identified on the date January 23, January 31 and February 1, respectively. In mid-March 2020, Italy became the highly infected country across the globe. At the end of March 2020, the USA became the leading country having majority of COVID-19 positive cases. The number of total cases up to April 17 was 632,781 (USA), 168,941 (Italy) and 13,387 (India) with numbers of mortality 28,211 (USA), 22,172 (Italy) and 437 (India) [14].

The initial growth rate of SARS-CoV-2 cases was almost similar in these countries. However, after 6-8 weeks period, the rate of progression surprisingly increased in the USA and Italy as compared to India. Therefore, it appears rational to identify the possible reasons for the limited disease progression in India.

PROGRESSION OF THE DISEASE

From the date of the first confirmed COVID-19 case reported to the 5th week, the pattern of disease progression was slow in all 3 countries. However, from the 6th week onwards, there was a gradual increase in the number of cases in Italy, whereas, India and USA had relatively reduced the number of cases up to 8 weeks. From the 8th week onwards, the number of cases increased exponentially in the USA, which was more than the total number of cases in India and Italy (Fig. **1**). At the end of the 11th week, the total number of cases in the USA, Italy, and India was 363,321, 165,155 and 13,387, respectively. At the moment, the total number of reported cases in USA, Italy, and India is 632,781, 168,941 and 13,387, respectively.

CHAPTER 7

COVID-19 Altered Immune Signalling Pathways

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Abstract: Many COVID-19 patients die not just because of the virus but also due to the patient's own immune system responding in an exaggerated manner called "Cytokine Storm". This stormy strong immune response not only just kills the virus but also kills the patients. The interaction of COVID-19 with the immune system is poorly understood. Recently, some studies have indicated the alteration of innate and adaptive immune signalling pathways after COVID-19 infection. Thus, in this chapter, we have compared the normal immune signalling pathways with COVID-19 altered immune signalling pathways, which will help the researchers in the designing and development of specific drugs or vaccines against this virus.

Keywords: Adaptive immune system, COVID-19, Innate immune system.

INTRODUCTION

The immune system is a collection of organs and special cells that help to protect the body against pathogenic substances. This system is generally divided into two main types, *i.e.*, innate and adaptive immune systems. The innate immune system comprises physical (skin and mucous membrane), chemical (lysozyme), and cellular (macrophages, neutrophils) components that protect against the pathogens through activation of various signalling pathways. If the innate immune system is unable to handle the foreign substances, then the adaptive immune system is activated, which consists of T and B cells. Overall, the immune system is one of the complex systems of the body, which involves various signalling pathways. The understanding of the signalling of the immune system, particularly in disease conditions, could be helpful to develop new preventive and therapeutic approaches [1].

COVID-19 caused by SARS-CoV-2, which has spread worldwide and declared a global health emergency. The SARS-CoV-2 has an approximately 79% similarity

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index with the horseshoe bats [2], and there is an 80% similarity with SARS-CoV genes. The most common symptoms observed in patients of SARS-CoV-2 are fever, difficulty in breathing and bilateral lung infiltration, which are almost similar to any other viral infections [3, 4]. Hence, it is difficult to diagnose based on symptoms.

It has been observed that persons with better immunity have more chances of survival from the COVID-19 infection than immune-compromised patients. The patients who are already suffering from diabetes, hypertension, or any other cardiovascular disease are more prone to death due to COVID-19 infection [5, 6].

However, immune response plays a vital role in infectious disease, but the exact mechanism of COVID-19 altered immune signalling pathways is still unclear. Plentiful literature is available on SARS-CoV altered immune signalling pathways, which might help understand the alteration of immune response due to COVID-19. Thus, in this chapter, we have compiled the information related to COVID-19 altered innate and adaptive immune signalling pathways, providing supportive ideas for the researchers to plan effective drugs or vaccines against it.

COVID-19 ALTERED INNATE IMMUNE RESPONSE SIGNALLING PATHWAYS

Innate immune signalling is activated when any foreign substances like bacteria, fungi, viruses, *etc.*, enter the body. The normal innate immune signalling and its alteration after COVID-19 infection are explained in detail below:

Effects on Macrophages

In normal condition, when any pathogen enters the body, monocytes are activated and sense the pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs), and activate signalling cascades, which leads to the generation of inflammatory cytokines like TNFα, IL-1β, MIP-1α, *etc.* as shown in Fig. (**1**). Finally, all these mediators together destroy the pathogens. Macrophages are primary immune cells of the defense system, which are also activated in response to an infection and do the destruction of pathogens through the process of phagocytosis [1].

The COVID-19 virus enters the body, and the spike protein of the virus attaches to the host cell. Simultaneously, the innate immune system senses the PAMPs of this virus through PRR, which results in the activation of innate immune signalling pathways. However, in the case of COVID-19 infection, the activation of the innate immune signalling pathways results in uncontrolled production of TNFα, IL-1β, MIP-1α, *etc.* The uncontrolled release of cytokines results in septic

shock and death of the patients, as shown in Fig. (**1**). Recently, Mehta *et al*. [7] reported the alteration of innate immune signalling pathways after COVID-19 infection that finally results in the uncontrolled release of cytokines. In clinical cases, a number of deaths in COVID-19 patients have been reported due to cytokine storm.

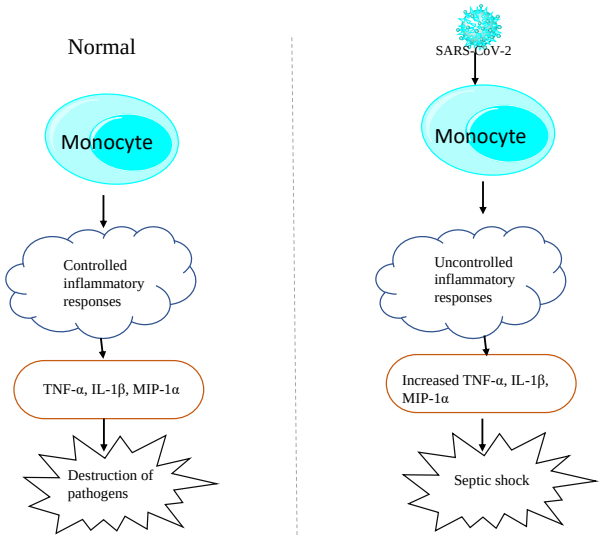

Fig. (1). Normal and SARS-CoV-2 altered innate immune response signalling pathways.

Effects on TLR Signalling Pathways

Toll-like receptors (TLRs) are highly found in cells like macrophages, dendritic cells, and neutrophils. The main function of TLRs is to sense the pathogen, which results in the activation of the transcription factors like MAPK, nuclear factor-kB (NF-kB), *etc.*, *via* the activation of MyD 88 dependent signalling and MyD 88 independent signalling pathways [1]. In the case of viral infections, finally, specific antiviral molecules like interferons (IFNs) are produced.

In humans, a total of 10 numbers of TLRs are known till now. Except for TLR3, all TLRs induce intracellular signalling pathways through the enrolment of the myeloid differentiation factor 88 (MyD88) receptor, while TLR3 activates the MyD 88 independent signalling cascades. TLR4 induces both MyD 88 dependent signalling and MyD 88 independent signalling cascades [8]. RNA viruses are normally sensed by TLR3 and TLR7 [9]. Recently, Prompetchara *et al*. [10] reported the sensing of COVID-19 through TLR3 and TLR7. Further, it may lead to the activation of further downstream signalling molecules, which is explained below in detail:

CHAPTER 8

COVID-19 Altered Brain Signalling Pathways

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Abstract: Coronavirus, an infectious disease known as COVID-19, has become a pandemic affecting the respiratory system of humans and leads to fatal outcomes. It has been originated from Wuhan, China, and has spread all over the world. This virus shares similar clinical symptoms with the earlier viral infections, such as Severe acute respiratory syndrome (SARS-Cove) and the Middle East respiratory syndrome (MERS-CoV) infection; therefore, COVID-19 is also known as SARS-CoV-2. As of SARS-CoV, SARS-CoV-2 also utilizes the ACE-2 receptor to enter the host cell. These receptors are reported to present in the brain and cerebrospinal fluid. Moreover, various COVID-19 patients reported symptoms related to neuro, such as nausea, headache, tremor, *etc.* This finding shows that the virus is not only restricted to the respiratory system, but it also invades the CNS, which raises the interest to find its mechanism to enter the human brain cell and alteration of various brain Signalling pathways such as interferon, MAPK, JAK-STAT, and ACE-2/ANG-(1-7)/MAS caused by the novel coronavirus. Here, in this chapter, the recent updates regarding COVID-19 brain alterations and the possible brain targets to treat the SARS-CoV-2 disease have been discussed.

Keywords: ACE-2, COVID-19, CNS, JAK-STAT, MAPK, SARS.

INTRODUCTION

In December 2019, a restricted pneumonia occurrence with an initial unknown cause was detected in Wuhan, China, and spread around the world. It was effectively found to be caused by a novel virus, which later on was identified as a new and evolved member of the coronavirus family as SARS-1, MERS, NL-63, and others. The virus was named severe acute respiratory syndrome coronavirus 2, *i.e.*, SARS-CoV-2, and the disease associated with it is called COVID-19 [1].

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The novel coronavirus-related infections were declared as a "Public Health Emergency of International Concern (PHEIC)" in the mid of January 2020 by the World Health Organization (WHO) [2].

SARS-CoV-2 has a genome of positive-sense single-stranded RNA and has a similar envelope to SARS-1. Reports from the recent research on genome sequencing and similarity suggest that the source of origin of this virus could be bat [3], as coronavirus from bats associates high similarity as 96% [4]. Most of the members of the coronavirus family (CoVs) share the same structure and pathway of infection. Like SARS-1CoV, SARS-2 CoV also uses ACE2 receptors to enter the cells. These receptors are in particular expressed by cells of airway epithelia, kidney, vascular endothelia, and brain [5, 6]. It has been found that in addition to systemic and respiratory symptoms, some of the COVID-19 patients have intracranial infections like symptoms such as headache, altered consciousness, and epilepsy [7, 8]. Sudden smell and taste loss were also reported in patients [9]. In the brain, ACE2 receptors are found on the surface of glial cells and neurons, explaining the reactive astrogliosis and activation of microglia in COVID-19 patients [10]. SARS-2 has been found in cerebrospinal fluid (CSF) [11]. Many published reports by clinicians across the world are listing anosmia, dysgeusia encephalitis, and severe hypoxia as symptoms of COVID-19, along with the more general respiratory symptoms [3, 12]. According to reports, 40% of COVID-19 patients have headaches, disturbed consciousness, and other brain dysfunctioning symptoms [3], and from autopsy reports, edema has been detected in the brain tissue of COVID- 19 patients [13]. CoV infection is also known to cause cytokine syndrome, which could be the possible reason for acute cerebral disease [14, 15].

A distinctive report by Mao *et al*., 2020 also reveals that in some patients, respiratory symptoms are preceded by neurological symptoms [16]. Preclinical studies on transgenic mice also revealed that when SARS-CoVis administered intranasally, it enters the brain *via* olfactory nerves and spread to some specific parts, like the thalamus and brainstem. It has also been observed that in mice infected with low inoculums dose of MERS-CoV, virus particles are detected only in the brain rather than lungs, indicating that infection in CNS was more responsible for the high mortality of mice due to MERS [10].

Given the huge implication of SARS-2 across all the continents for the years to come, it is very important to analyze the complete pathophysiology of the virus and the disease caused by it. This chapter, in particular, discusses the SARS-2 related neuropathology.

NEUROPATHOLOGY OF COVID-19

The blood-brain barrier (BBB) is the first line of defense that prevents the entry of pathogens into the brain, and it is composed of cerebral microvascular endothelium, pericytes, astrocytes, and extracellular matrix [17, 18]. Most of the neurotropic viruses enter the bloodstream after a sufficient titter of virus (viremia) reaches CSF [19]. From here, the virus crosses the BBB by trans endothelial pathway or transcytosis by endocytic vesicles through brain microvascular endothelial cells (BMECs) or *via* pericytes [20]. Further, the systemic infection by some viruses releases inflammatory mediators like cytokines and chemokines, which also disrupt the integrity of BBB [21].

As discussed above in the introduction, COVID-19 disease has several neurological symptoms besides respiratory symptoms; thus, a complete understanding of the neuropathology of the SARS-2 is an ultimate necessity [22, 23]. Keeping the published reports of various other viruses in mind, it is hypothesized that the SARS-2 can enter the brain *via* the following five mechanisms (Fig. **1**).

Direct Pathway

The mechanism of the coronavirus to invade CNS can be through direct infection, which further includes blood circulation pathway neuronal pathways (*via* the olfactory nerve).

a. Blood Circulation Pathway

Till now, there are no reported studies about studying the neuropathology of SARS-2 however, studies for many other viruses report that viral genetic material and proteins are found in the tissue samples of the nervous system (*e.g.*, CSF and other brain tissues), indicating that the viruses can enter the CNS and can cause nerve cell destruction [7, 23]. In the blood circulation pathway, when the virus is released into the blood circulation, it reproduces inside the mononuclear macrophages and stimulates the production of inflammatory mediators like cytokines, which enhances the BBB permeability by disrupting its cells leading to opening a path for the virus to enter the brain [24].

b. Neuronal Pathway

The neuronal pathway is also one of the paths taken by many neurotropic viruses to invade the CNS [25]. In this pathway, migration of the viruses in the CNS can be achieved by the virus by infecting the sensory or motor nerve endings through

CHAPTER 9

Risk Factors and Complications Associated with COVID-19

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Abstract: The global pandemic situation of COVID-19 has drawn the attention of various health care professionals. Several preclinical or clinical investigations have been explored; however, effective management of COVID-19 has not been found yet. The infection to death ratio related to COVID-19 varies in different countries, yet endangering human survival. Therefore, at present, prevention from SARS-CoV-2 infection appears promising in limiting the spread of the disease. The susceptibility of different individuals varies extensively in a demographic distribution. It has been found that patients with cardiovascular or metabolic disorders, smoking habits, and health care professionals have a higher susceptibility towards SARS-COV-2 infection.

Therefore, it becomes mandatory to spread awareness to the people who are at higher risk. After COVID-19 infection, the occurrence of several complications may be life-threatening. Thus, this review has summarized the information regarding the susceptibility of people towards COVID-19 disease and disabling/life-threatening conditions after getting infected from COVID-19 disease.

Keywords: ACE, COVID-19, Diabetes mellitus, Hypertension, Risk factors, SARS-CoV-2.

INTRODUCTION

COVID-19 is a worldwide pandemic that appears to be associated with a high death toll. World Health Organization (WHO) announced COVID-19 as a public health emergency of international concern on 31st January 2020 [1]; however, initial cases of COVID-19 were identified in December 2019 in Wuhan city, China. All patients were linked to the Wuhan seafood and wet animal wholesale market [2].

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The major reason for the spread of this virus is human-to-human transmission *via* close contact. It is clear that COVID-19 infection occurs through interpersonal contact with the virus in normal and immunocompromised persons [3]. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV [2]. The COVID-19 has been found to have higher levels of transmissibility and pandemic risk than the SARS-CoV outbreak [3]. Currently, approx 7 million COVID-19 cases and 3.2 million deaths have been recorded worldwide. Recently, India has become the 6th leading country with a higher number of COVID-19 patients.

The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days [4]. The period from the onset of COVID-19 symptoms to death ranges from 6-41 days, with a median of 14 days [5]. Among all the patients, the most common symptoms are fever (94%), cough (79%), sputum (23%), myalgia (15%), and fatigue (23%). Apart from these, diarrhoea, nausea, vomiting, and sore throat have also been found [6]. The symptoms of the COVID-19 are similar to a common cold, so patients easily ignore the initial symptoms. Clinical features revealed by a chest computerized tomography (CT) scan presented pneumonia with other abnormalities like acute respiratory distress syndrome (ARDS), cardiac injury and incidence of grand-glass opacities (GGO) that may cause death. In other cases, multiple peripheral ground-glass opacities were observed in sub-pleural regions of the lungs [2].

Patients infected with COVID-19 show elevated leukocyte numbers, abnormal respiratory findings, and augmented levels of plasma pro-inflammatory cytokines. Moreover, there is an increase in the blood C-reactive protein levels, and erythrocyte sedimentation rate and D-dimer are also observed [7]. The main pathogenesis of COVID-19 infection is severe pneumonia because it targets the respiratory system. Detectable serum SARS-CoV-2 viral load, combined with the incidence of GGO, and acute cardiac injury, have also been found in COVID-19 patients. Significantly, elevated levels of cytokines and chemokines and vascular endothelial growth factor A have been noted in patients with COVID-19 infection. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines, including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα, which were found to be associated with the severity of the disease [8]. The exact pathology of SARS-CoV-2 infection is not clearly understood; however, the previous information of SARS-C0V and MERS-CoV has proven useful to tackle with COVID-19 infection.

The degree of CoV infection depends upon its attachment and entry into the host cell. In this process, the envelope spike glycoprotein binds to a number of cellular receptors for the entry, like angiotensin-converting enzyme-2 (ACE-2) receptor is

the most common for SARS-CoV and SARS-CoV-2, which facilitates the virus entry and its replication inside the host cell. CD209L (a C-type lectin, also called L-SIGN) is specifically recognized by SARS-CoV and DPP4 for MERS-CoV [9]. Studies also indicate that SARS-CoV-2 interacts more efficiently with the ACE-2 receptor than SARS-CoV, suggesting the reason for the high transmission of this virus. ACE-2 is a type 1 integral membrane glycoprotein that is constitutively expressed by the epithelial cells of the lungs, heart, kidney, intestine and blood vessels. The role of ACE-2 receptor is not only to facilitate the entry of the virus but it also has a critical role in the protection of the lungs from injury. Thus greater lung damage may be defined based on the degradation of the lung-protective mechanism [10].

SARS-CoV-2 uses the trans-membrane protease serine 2 (TMPRSS2) for the spike priming, which is essential for the entry and its virulence through the interaction of ACE2 receptors [11]. Once the virus enters inside the cell, it releases the viral RNA genome into the cytoplasm that is translated into two polyproteins and structural protein. Then viral genome begins to replicate and forms all the structural components of the virus. Then nucleocapsid is formed by the combination of genomic RNA and nucleocapsid protein. The viral particles then germinate into the endoplasmic reticulum-Golgi intermediate compartment. At last, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus [12].

At present, there is limited knowledge available about the host and SARS-CoV-2 innate immune response. After SARS-CoV-2 infection, an increase in total neutrophils, IL-6, c-reactive protein and a reduction in total lymphocytes are observed [6]. Either direct or indirect activation of immune response mimics the sepsis, shock-like condition in the infected individuals, making them more vulnerable to multiple organ failure and mortality. Still, there is no sufficient information about how cells specific antigens are produced in SARS-CoV-2 infection, but we can take little information from previous CoVs like SARS-CoV in which antigen presentation mainly depended on major histocompatibility complex (MHC) I and MHC II [13].

Activated T cells start to differentiate and produce a large amount of cytokines and different T cell subsets like T helper 17 (Th17). Due to the great viral load and continuous production of these mediators, the virus inhibits the natural killer cells, CD8 cells and T cell activation. However, CD8 T cells produce very effective mediators to clear CoV [14]. There may be the production of specific antibodies against SARS-CoV-2 by B cells, which may help to neutralize the viruses. Other B cells/plasma cells produce SARS-CoV-2 specific antibodies that may help neutralize viruses. On the other hand, type I IFN appears protective as a

CHAPTER 10

Possible Mechanism of Deaths Due to COVID-19

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Abstract: The novel coronavirus disease 2019 (COVID-19) is an acute infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). After severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), COVID-19 is the third acute infectious disease caused by the coronavirus in humans. According to WHO, as of 3rd March 2020, the mortality rate of COVID-19 cases was reported globally as approximately 3.4% and it was observed particularly in patients who were suffering from comorbid conditions. The exact mechanism of death is unclear so far, however, emerging reports have indicated that less oxygen supply, excessive release of cytokines, and inflammatory mediators could be one of the reasons. Thus, in this chapter, we have provided classification of death cases occurring due to COVID-19. The possible mechanism of death is also discussed. The last section of the chapter discusses the role of concomitant medication in the death of COVID-19 patients.

Keywords: 2019-nCoV, Coronavirus disease 2019, Cytokine storm, Pandemic disease, SARS-CoV-2.

INTRODUCTION

On 31st December 2019, in Wuhan, Hubei Province, China, a cluster of pneumonia cases have been reported in people associated with the Huanan Seafood Wholesale Market. On 7th January, 2020, Chinese health authorities confirmed the association of these cases with the novel coronavirus (2019-nCoV) [1]. Although these cases were originally reported to be associated with exposure to the Wuhan seafood market, current epidemiological data indicate that the 2019-nCoV human to human transmission occurs due to which the infection has spread rapidly throughout China and many other countries. On 11th February, 2020, a new name was announced for the temporarily named 2019-nCoV epidemic by

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The World Health Organization (WHO) as coronavirus disease-2019 (COVID-19) [2], whereas the International Committee for Taxonomy of Viruses renamed the previous provisionally named 2019-nCoV as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [3]. SARS-CoV-2 differs from SARS-CoV, which was responsible for the outbreak of SARS in 2003, and MERS-CoV, which was responsible for the ongoing outbreak in the Middle East in 2012. The presentation of COVID-19 ranges from asymptomatic to severe viral pneumonia, acute respiratory distress syndrome, and even death [4]. Following influenza A virus subtype H1N1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016), and Ebola in the Democratic Republic of Congo (2019), COVID-19 was declared as the sixth public health emergency of international concern by WHO on 30th January 2020 [5].

According to the WHO, 3,588,773 cases of COVID-19 were confirmed on 6th May 2020 (10.00 pm CET), and 247,503 patients died globally [6] and the virus became a global health problem that caused serious human respiratory tract diseases. Human to human transfer has been declared to facilitate its spread through droplets, contaminated hands or surfaces, with its incubation time ranging from 2-10 days [7]. However, the knowledge of a possible mechanism of death due to COVID-19 is an open question for researchers to answer. This chapter presents the distribution of death cases in COVID-19 in India and across the globe along with the possible mechanism of death.

DISTRIBUTION OF DEATH CASES DUE TO COVID-19

In India, the first case of COVID-19 was reported on 30th January 2020 while the first death was reported on 12th March 2020. As of 7th May 2020 (8:00 IST), there were 52,952 confirmed cases due to COVID-19, among which 15,267 cured/migrated and 1,783 died (70% of cases were due to comorbidities) in India, according to the Ministry of Health and Family Welfare [8]. In India, the maximum number of deaths occurred in Maharashtra (651) followed by Gujarat (396), Madhya Pradesh (185), West Bengal (144), Rajasthan (92), Delhi (65), Uttar Pradesh (60), Andhra Pradesh (36), Tamil Nadu (35), Karnataka (29), Telangana (29), Punjab (27), Jammu & Kashmir (8), Haryana (7), Bihar (4), Kerala (4), Jharkhand (3), Himachal Pradesh (2), Odisha (2), Assam (1), Chandigarh (1), Meghalaya (1), and Uttarakhand (1) till 7th May 2020. The state-wise data of total confirmed cases, cured/migrated/discharged cases, and total deaths are compiled in Table **1** [8]. Globally, the maximum number of deaths were found in the United States of America (62,698), followed by the United Kingdom (29,427), Italy (29,315), and Spain (25,613) till 6th May 2020 [6].

Analysis of age profiling for COVID-19 positive cases revealed that 9% of cases

were between 0-20 years; 42% were between 21 to 40 years; 33% were between 41 to 60 years, and 16% cases were of above 60 years, as shown in Fig. (**1**). Thus, individuals of any age may acquire SARS-CoV-2 infection, but adults of middle age and old age are most frequently affected, and older patients are more likely to develop severe illness.

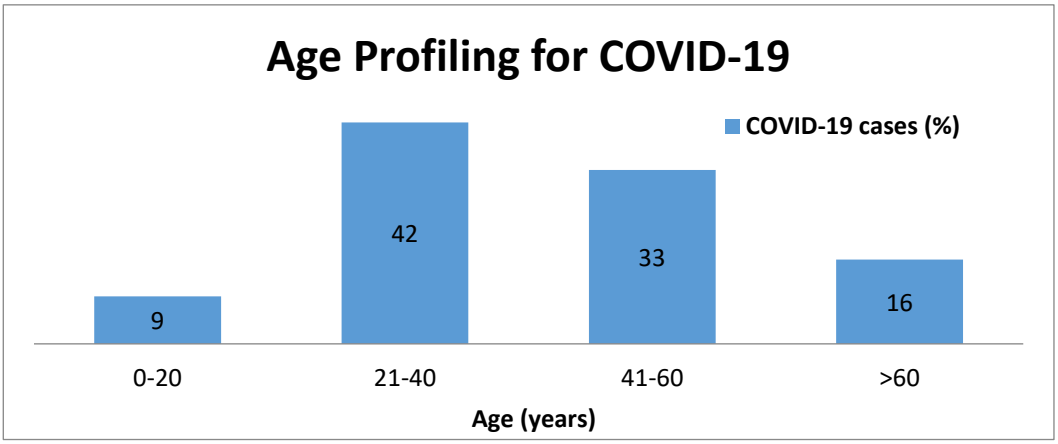

Fig.(1). Age profiling for COVID-19.

POSSIBLE MECHANISM OF DEATHS WITHOUT TREATMENT

SARS-CoV-2 belongs to the beta coronavirus as SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses [9].

The functional receptor for coronaviruses, including SARS-CoV and SARS-CoV-2, is angiotensin -converting enzyme 2 (ACE2) which is highly expressed in the heart and lungs [10]. SARS-CoV-2 infection is triggered by the binding of the spike protein of the virus to ACE2. It can enter through the eyes, nose and/or mouth and make way into the respiratory tract, multiply in cells lining the airway, damaging the lining of air passages, thus causing inflammation. It also irritates the nerves in the lining of the airway, resulting in respiratory symptoms. However, when the infection gets worse, the virus enters the gas exchange units, alveoli, and triggers inflammation. Further, it reacts by outpouring the inflammatory material, *i.e.* fluid and inflammatory cells into the lungs, causing pneumonia. As the lungs get filled with inflammatory material, enough oxygen is not able to enter bloodstream and get rid of carbon dioxide. Finally, it results in the death of the patient with severe pneumonia. Pneumonia caused by COVID-19 is different from that of usual pneumonia caused by bacteria as coronavirus pneumonia affects the entire lung, instead of a small section called acute respiratory distress syndrome (ARDS). The development of hypoxia, ARDS, and septic shock further leads to

CHAPTER 11

Possible Targets of SARS-CoV-2

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Abstract: Recently, the World health organization (WHO) has declared COVID-19 as a global health emergency as it is spreading almost all over the world. The number of infections to death ratio related to COVID-19 is varying in different countries, yet endangering human survival. Currently, no specific treatment is available, thus, there is a need for specific drugs against SARS-CoV-2. To develop specific drugs, specific targets should be identified. Thus, this chapter summarizes potential targets in SARS-CoV-2.

Keywords: Anti-SARS-CoV-2 drug discovery, COVID-19, Potential Human cell targets, Potential SARS-CoV-2 targets.

INTRODUCTION

The recent concern of the pathogenic 2019 coronavirus in China (Wuhan) has led to a major outbreak and its rapid National and International widespread made the WHO to officially declare this pandemic as a global public health emergency [1, 2]. On 11th February 2020, the International Committee on Taxonomy of Viruses (ICTV) announced the name of this novel virus as "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)". This name was selected as it is genetically related to the CoV (coronavirus) responsible for the SARS outbreak which occurred in 2003. The World Health Organization (WHO) chose "coronavirus disease (COVID-19)" as the name of this disease following guidelines earlier developed with the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE). There were approximately 7,50,890 confirmed cases and 36,405 deaths cases worldwide as of 31st March 2020 [3]. Despite so many deaths globally, no treatments/therapies have still come to existence; yet, the knowledge gained from

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the extensive research and development efforts may aid the current therapeutic options based on the target approaches.

SARS-CoV-2's genome (~30kb) has G+C contents ranging from 32-43%. It contains positive single-stranded RNA with 5'-cap and 3'-poly-A tail, belonging to the order of *Nidovirales*, a family of *Coronaviridae,* and subfamily *Coronavirinae* [3]. The subfamily *Coronavirinae* is further divided into four genera *i.e.* α, β, γ, and δ whereas the SARS-CoV-2 is grouped under β genus [3]. The genomic RNA of virus result SARS-CoV-2 result in the production of two polyproteins (pp) precursors corresponding to open reading frames *i.e.* ORF-1a (called pp1a) and ORF-1b (called pp1ab) through the translational process.

Further, these pp (pp1a and pp1ab) present almost 2/3rd part of genome length near 5' terminal are intercellularly processed by virally encoded proteins like 3 chymotrypsin-like protease (3CLpro) or main protease (Mpro) and one or two papain-like proteases (PLpro) to yield functional 16 non-structural proteins (nsps) [6, 7]. Besides, these nsps are assembled with cellular components to form a replication/transcription complex (RTC) associated within double-membrane vesicles (DMVs) derived from the endoplasmic reticulum (ER) as shown in Fig. (**1**) [3, 4]. Also, RTC transcribes a nested set of subgenomic RNA(sgRNAs) in a discontinuous manner along 5'- 3' ends [8]. Genomes and sub-genomes of CoVs contain at least 6 ORFs amongst variable numbers (6-11) of small ORFs which are present in various conserved genes [4, 5].

The hydrophobic transmembrane domains present in nsp3, nsp4 and nsp6 help to anchor the pp1a and pp1ab to membranes after RTC formation. Other ORFs present on the 1/3rd of the genome near the 3' terminal encodes accessory protein (interfere with host innate immune response) and structural proteins like a spike(S), envelope(E), membrane(M), and nucleocapsid (N) proteins [7]. Besides these main structural proteins, different CoVs encode special structural and accessory proteins, such as hemagglutinin-esterase protein, 3a/b protein, and 4a/b protein from the sgRNAs. The functions of individual structural proteins and Nsps are described in Table **1**.

The potential anti-SARS-CoV-2 drugs can be classified into two main divisions depending on the target, one acting on the human cells, and the other on the virus itself. The innate immune system response of humans plays a vital role in controlling the infection and replication of the pathogenic virus. Cytokines act as chemical signals to invade the pathogen. Specific types of cytokines that contribute to eliminate the pathogen are lymphokines, interferons (IFNs), interleukins, and chemokines.

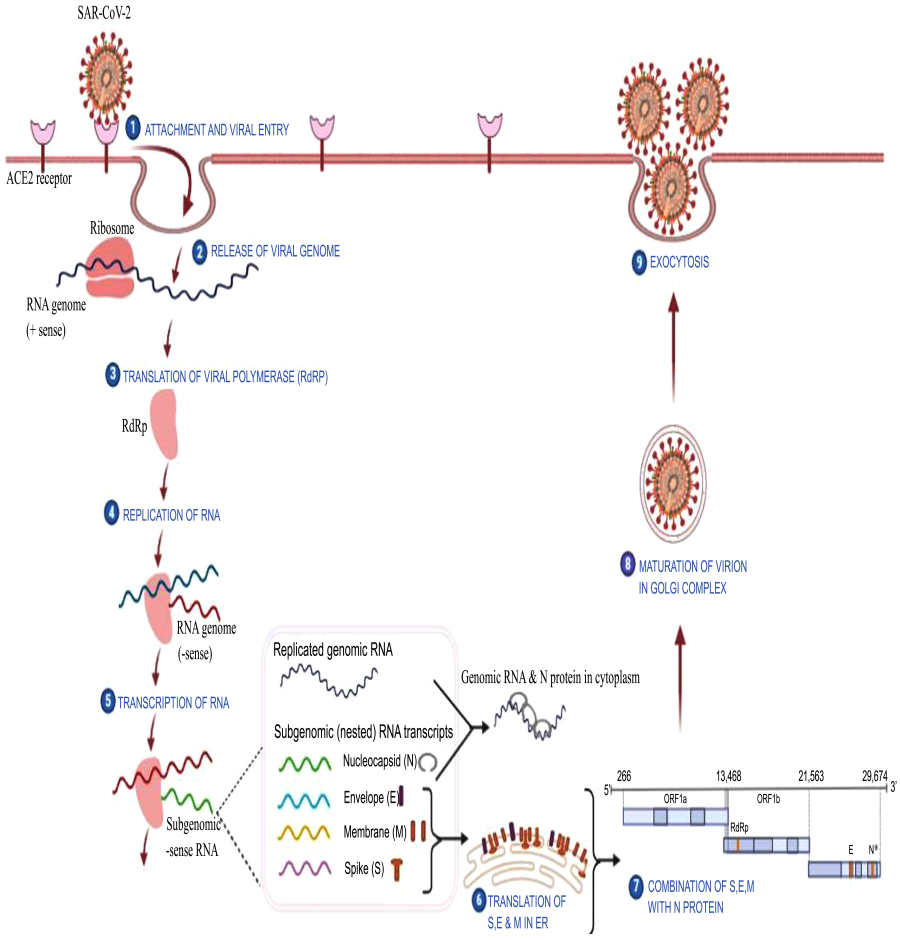

Fig. (1). Possible targets of coronavirus 2019 (COVID-19).

The most prominent among them are IFNs (Type I, type II, and type III). The IFN's and IFN fusion proteins are used as anti-viral therapeutic agents [8]. Also, viruses usually bind to surface cell receptors to make an entry into the host. The attachment of the viral protein to the host cell receptor is the crucial step in the replication cycle and this step defines the degree of virology of the virus. Thus, the efficiency of the viral infection is strongly dependent on its entry to the cell. There is valid scientific evidence, which showed that spike proteins, which are present on the surface of the virus, interact with angiotensin-converting enzyme 2 (ACE2) a receptor that helps for attachment and entry into the cell. Some other

CHAPTER 12

Repurposing of Drugs for COVID-19 Infections

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Abstract: In December 2019, the sudden emergence of severe respiratory disease caused by novel coronavirus-2019 in Wuhan City, Hubei Province, China has become a public health emergency. As of June 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 9,000,000 and mortality of more than 450,000 individuals, leading to devastating consequences worldwide. The persistent human-to-human transmission of nCoV-19 has prompted scientists to develop the treatment for coronavirus disease 2019 (COVID-19). Moreover, it has been declared as a pandemic and there is an urgent need for the development of treatment. However, there is no specific and effective treatment approved against COVID-19 to date. Developing a new drug is a time-consuming process, which is impractical to face the immediate global challenge. Thus, drug repurposing or drug repositioning is a strategy that allows the use of existing molecules against new indications. This chapter summarized various drugs repurposed against coronavirus disease 2019 along with the current challenges and future perspectives of drug repurposing against COVID-19.

Keywords: Coronavirus, Coronavirus disease 2019, Drug repositioning, Drug repurposing, Novel coronavirus-2019, Pandemic, Severe acute respiratory syndrome coronavirus 2.

INTRODUCTION

In December 2019, in Wuhan City, China, the emergence of severe respiratory disease with pneumonia-like symptoms caused by novel coronavirus 2019 (COVID-19) became a threat to public health and the economy worldwide [1]. Currently, there is no specific treatment available against coronavirus disease 2019 (COVID-19), only supportive care is available. However, the availability of specific and effective treatment against COVID-19 will be of benefit to fight against this pandemic disease. Developing a new drug from scratch takes decades

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to come to the market and is an expensive process being impractical in the current situation. Thus, there is a need for an alternate method to reduce time, cost, and improves success rates.

Drug repurposing, also known as drug repositioning is a drug development strategy in which already existing molecules are reused to treat a new medical condition. As its existing molecules, so we know the behaviour of molecules including its pharmacokinetic and safety profile which reduce the time and money involved in the drug development process [2]. Therefore, recently, many studies have focused on the repurposing of clinically available drugs against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this chapter, we have discussed molecules which are repurposed or can be repurposed in the treatment of COVID-19 infection. Further, current challenges and future perspectives of repurposing drugs against novel coronavirus 2019 (COVID-19) have also been discussed.

REPURPOSING OF DRUGS AGAINST SARS-COV-2

SARS-CoV-2 is a single-stranded, enveloped, positive-sense RNA virus [3]. There are spike proteins (S proteins) present on SARS-CoV-2 as protrusions from the surface, giving the virus crown-like appearance, hence the name "coronavirus".

Recently, to repurpose existing drugs against SARS-CoV-2, scientists are exploring the druggable targets effective against the virus [4]. The life cycle of coronavirus (Fig. **1**) depicts various potential targetable proteins such as angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) responsible for the endocytic entry of SARS-CoV-2 inside the host cell; helicase and RNA-dependent RNA polymerase (RdRp) which are involved in RNA replication; chymotrypsin-like and papain-like proteases helping in translation and proteolytic processing of virus [4, 5]. The other sites that can be targeted the assembly of virion and new virus release through exocytosis [3]. The understanding of the detailed viral structure and its replication mechanism can help to explore further potential targets against novel coronavirus 2019 (COVID-19).

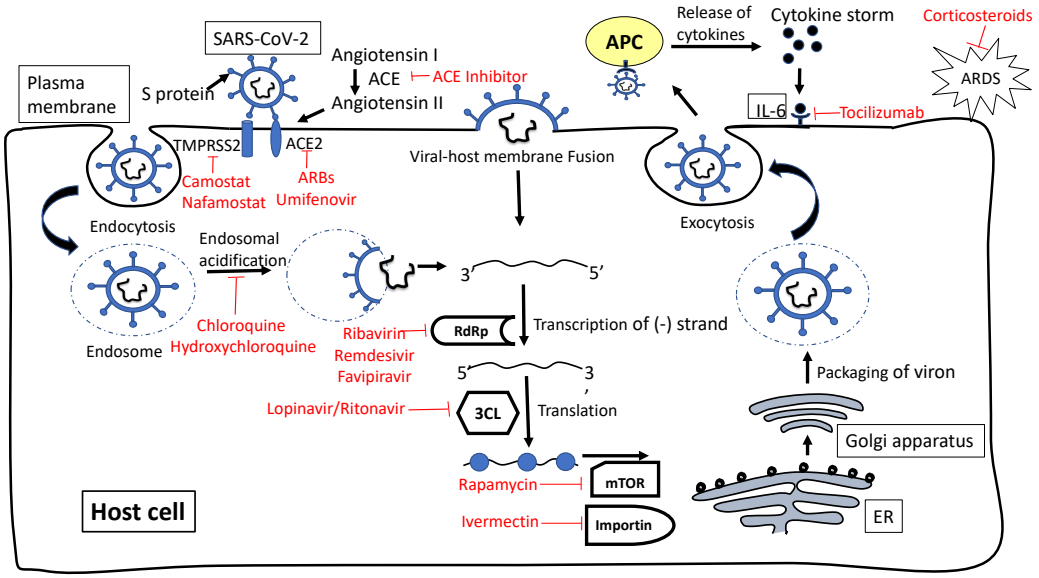

Fig. (1). Potential antiviral mechanism of repurposed drugs against SARS-CoV-2.

The various drugs repurposed for COVID-19 are discussed in detail below:

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are well known antimalarial agents having similar structures and mechanism of action. Both of these drugs alter the endosomal function and show their antimalarial activity by blocking autophagosome-lysosome fusion [6]. As antiviral, chloroquine and hydroxychloroquine have multiple mechanisms of action and hence repurposed against COVID-19 infection. It has been observed that chloroquine affects the post-translational modifications of the transmembrane viral binding proteins, impairing viral penetration inside the cell [7, 8]. Thus, prevent uncoating of viral envelop and release of RNA in host cell cytoplasm by raising the pH of acidic vesicles (endosomes) [9 - 16]. Moreover, viral replication, assembly, and release are also impaired by chloroquine [9, 11]. Various reports have also shown the impairment of the glycosylation of ACE2 after chloroquine treatment. Thus, interrupting the interaction between S proteins and ACE2 [17, 18] and blocking their entry inside the host cell. Further, chloroquine enhances viral antigen presentation, thus increasing T-cell mediated immunity [19]. Overall, chloroquine and hydroxychloroquine show their antiviral activity against COVID-19 infection through inhibition of multiple targets as shown in Fig. (**1**). Hydroxychloroquine is more preferable over chloroquine due to its safe and effective profile.

CHAPTER 13

Herbals for COVID-19 Infection

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Abstract: Herbals are used from ancient times for the treatment of various body ailments. These are also used in the treatment of various infectious diseases, including viral infection. Recently, COVID-19 viral infection has emerged and spread across the globe. Currently, no specific drugs are available in the treatment of this infection. Thus, there is a need for specific drugs or herbal molecules against this infection. This chapter summarized potential antiviral herbals that could be effective in the treatment of COVID-19 infection. Further, the proposed mechanism of action of these herbals against COVID-19 has also been discussed. Finally, this chapter concludes with current challenges and the future perspectives of using herbals against COVID-19 infections.

Keywords: Antiviral activity, COVID-19 infections, Herbals, Herbal molecules, Mechanisms.

INTRODUCTION

Herbal therapy can be defined as the application of medicinal plants for various therapeutic outcomes, such as treatment and prevention of various diseases and infections to promote the health status of an individual [1]. According to the World Health Organization (WHO), 80% of the total population uses herbal medicines to achieve a normal healthy life. Around 50% of the prescribed drugs are derived from plants only [2]. The herbal molecules which were used as food or raw material in the traditional system of medicines are more pharmacologically active because of secondary metabolites [3]. These herbal products not only increase the immunity of human beings but also play a vital role in the treatment of various ailments, such as common cold, allergy or hypersensitivity, toothache, GIT upsets, and other infectious diseases, *etc.* [4]. Herbal molecules are well

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known for their anti-oxidant, anti-inflammatory, anti-viral, anti-microbial, anti-parasitic, and anti-tumour activities [5].

As herbal medicines have fewer side effects, the number of patients seeking herbal therapy is growing day-by-day exponentially. Amongst the various infectious diseases, viral diseases are mainly the leading cause of death worldwide. A large number of phytoconstituents derived from medicinal plants are well known for their antiviral activity [6]. These herbal drugs are used for many years which helps in relieving various symptoms of diseases involving treatment of different viral infections, such as measles viruses, human rotaviruses (HRV) [7], respiratory syncytial virus (RSV) [8], human rhinoviruses, Japanese encephalitis virus [9], severe acute respiratory syndrome (SARS) [10], middle east respiratory syndrome (MERS) [11] and various strains of poliovirus [12]. These herbal products interact mainly with the pathogenesis and life cycle of the virus, inhibiting viral replication, or synthesis of a viral genome from exhibiting anti-viral action [13].

The importance of herbal therapy appeared when a severe acute respiratory syndrome (SARS) outbreak took place in 2003, affecting thousands of lives. Although a wide variety of vaccines and antiviral agents are available in the market to prevent and treat various viral infections, yet they are not proved as an effective treatments that can target these respiratory syndromes [14]. Recently, the world is facing a new pandemic called 2019-nCoV originated from Wuhan, China. This life-threatening respiratory disorder is affecting millions of lives all over the world. The researchers and scientists are continuously working to develop vaccines and medications against this virus [15]. However, none of them is succeeded yet. The herbal molecule could also play an important role in this pandemic situation. Thus, in this chapter, we have discussed the various potential herbals, which have antiviral activity against positive-sense single-stranded RNA viruses. Further, the proposed mechanism of action has also been discussed. Finally, this chapter concludes with current challenges and the future perspective of the use of herbals against COVID-19 infections.

HERBALS AGAINST SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

Severe acute respiratory syndrome (SARS) is one of the life-threatening viral respiratory disorder of zoonotic origin caused by one of the identified strain of the SARS coronavirus (SARS-CoV or SARS-CoV-2) which spread to various countries including Europe, North America, South America, and Asia in 2003 [16]. The virus has a single-stranded positive-sense RNA genome approximately 30 kb in length [17]. According to WHO, this pandemic has infected over 8,096

people worldwide and more than 774 people died with a mortality rate of about 9.6% of the total infected individuals [18]. SARS is mainly transmitted *via* infected water droplets across short distances among close contacts. Although indirect transmission is also possible, which is characterized by flu-like symptoms including sore throat, fever (above 38 °C or 100 °F), cough, shortness of breath, pneumonia, muscle pain, and lethargy [19]. The average incubation period for SARS is 4–6 days, but it can vary from 1 day to 14 days. Although multiple drugs have been reported in the literature which can attenuate this viral disease still there are no clinically approved antiviral drugs specified for SARS treatment [20].

Various naturally occurring tri-terpene glycoside such as saikosaponins B2 prevent early stages of infection through inhibition of viral attachment, and penetration [21]. The herbal extracts of *Artemisia annua*, *Lycorisradiata*, *Lindera* aggregate and *Pyrro sialingua* shows protective action against SARS-CoV infection. The aqueous extract of *Houttuynia cordata* blocks the viral RNA-dependent RNA polymerase and 3CL protease [22]. Apart from these, some of the natural inhibitors like myricetin, scutellarein, and isatisindigotica have also been reported in the literature for their antiviral activity through inhibition of 3CL protease and nsP13 helicase [23]. The various types of studies (*in-silico*, *in-vitro* and *in-vivo*) have been reported in the literature regarding the anti-SARS activity of herbal drugs which are discussed below:

In-Silico Studies

In literature, various computational techniques are used for the screening of herbal molecules against various targets of SARS. Shen *et al*. have reported 27 compounds like emetine, lycorine, mycophenola temofeti, mycophenolic acid, monensin sodium, harmine, pyrivinium pamoate, and phenazopyridine, *etc*. after the screening of 290 compounds which might be effective against SARS [24]. The docking studies are the most commonly used computational technique for the screening of compounds. Jo *et al*. have reported herbacetin, rhoifolin, pectolinarin as promising compounds against SARS-CoV after screening of a large number of natural compounds using induced-fit docking studies [25]. The flavonoids are also screened using computational docking studies against 3CLpro of SARS-CoV and quercetin, epigallactocatechingallate, gallocatechingallate are reported as promising compounds [26]. The Chinese medicinal herbs are also screened using computational methods and reported 3 promising herbs (Radix Polygonimultifori, Radix et RhizomaRhei and Caulis Polygonimultifori) belonging to the family Polygonaceae against SARS virus [27]. Wang *et al*. have screened natural compounds and reported MOL736 derived from *Artemisia annua* as a most promising compound against SARS-CoV [28]. The 3CLpro inhibitors of SARS are also identified after the screening of a large number of natural molecules

CHAPTER 14

Current Challenges and Future Prospects of COVID-19

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Abstract: The novel epidemic of zoonotic origin coronavirus disease (COVID-19) outbreak from wet market Wuhan, Hubei province of China became one of the massive eruptions toward humanity in 2020. In the present scenario, the World Health Organization declared the coronavirus outbreak as a public health pandemic. Researchers have been trying to develop vaccines and drugs against SARS since its outbreak, but no licensed treatments and vaccines are available. So, in the epidemic situation, consequently precautions measures are the only solution to prevent the spread of this virus. Scientists are struggling for vaccine development against COVID-19 that mainly targets the surface protein (S), the major inducer for neutralizing antibodies. Although few aspirants are also working for *in vitro* studies and many clinical trials are going on throughout the world. This chapter summarised the on-going challenges in the development of vaccines and specific drugs against SARS 2 along with future prospects.

Keywords: Biological disasters, Coronavirus, Epidemics, MARS-CoV, Respiratory syndrome, SARS-CoV, Viruses.

INTRODUCTION

Coronaviruses are a larger group of viruses that infect humans and recent, SARS 2 emerged from China become a major threat to the world. The virus spread rapidly from human to human but spread from species to species still a mystery. The Centre for disease control and prevention and the World Health Organisation made a COVID-19 website for daily updates regarding infection cases, recoveries, and deaths from all countries [1]. The extent of the ramifications caused is still unclear, but it is evident that the world has come to a standstill. Scientist making efforts for developing a vaccine and various drugs explored against COVID-19 infection, which is already used previously against Severe acute respiratory syndrome coronavirus (SARS), Middle East respiratory syndrome-related corona-

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virus Middle East respiratory syndrome-related coronavirus (MARS), Human immune deficiency virus (HIV), Malaria, Ebola, Nipah and Zika virus treatments [2]. Further, for ongoing research, these vaccines can be exploited due to their potency, efficacy, and safety to develop a potential COVID-19 vaccine. However, results have some limiting features; can be opted to discover valuable modalities for tackling the emerging COVID-19, but effective vaccine and treatment are still not available. A major reason for unavailability of licensed treatment for coronavirus can be lack of approval and commercialization of vaccine because outbreak affects few peoples so by the new vaccine discovery no patient remains available for clinical trials. Another reason can be the lack of interest of Pharmaceutical companies that vaccine and treatment demands last till these outbreaks last [2, 3]. So, the common law of remedies used as a therapeutic option for managing the COVID-19 treatment is based on the previous experience of treatments for MARS and SARS. The WHO recommended quarantine and travel ban and have been imposed globally. Therapeutic drugs like remdesivir, oseltamivir, ritonavir, and lopinavir alone or in combination with interferon-β have significantly been used to block the COVID-19 infection in patients. Recently, convalescent plasma and mAbs have also become a therapeutic trend for the treatment of infected patients [3]. Nevertheless, intense efforts are on-going for the discovery of licenced therapeutic of COVID-19. This chapter discusses the current challenges and future prospects of COVID-19.

FORTHCOMING CHALLENGES AGAINST COVID-19

Novel zoonotic origin epidemic comes out as a great human threat and challenge, but no licensed vaccine and drugs are available for its prevention and treatment. Despite the two major epidemic outbreaks of coronaviruses in past decades, vaccine and drug discovery are still in their infancy. Health care professionals have been confronted with several challenges as initial cases reported with direct contact to wildlife, but human-to-human spread not identified. Not even all hospitals have been equipped with sufficient protective gear due to the number of cases increased rapidly. Early detection and segregation of infected cases have been the bedrock for curbing the rapid spread of communicable diseases, but there was little knowledge of the origin of an outbreak [3]. However, earlier symptoms were similar to pneumonia, but currently, the disease named as novel coronavirus. Rapid human-to-human spread rises the cases and many Health care professionals also infected during patients' treatment neglectful of their consciousness. Initially, broad-spectrum vaccines and specific vaccines were used alone and in combination with antiviral drugs. Recently, doctors used plasma from clinically recovered patients of coronavirus and injected it to the patient showing symptoms for COVID-19 [4]. Rapid recovery was found in those patients. Meanwhile, the prediction impact of a pandemic depends upon the overall number of infections;

however; the total number still not estimated due to lack of diagnostic tests. The current pandemic brings into notice the shortage of clinical setting items, including; gloves, mask, sanitizer and bodysuits. However, in some countries shortage appears worse among special equipment for critical conditions including; intensive care unit (ICU) space, ventilators and beds and the economic power of countries also affected [4] (Fig. **1**). Countries authorities recognised that without shutting down normal life, the pandemic spreading is impossible to control. Therefore, complete lockdown, social distancing and quarantine options opted globally for interruption against transmission chain [5]. The current pandemic still not remediable and make a strong influence on the economic power of all countries. Therefore, we converse upcoming challenges to prevent, control, and eradication of pandemic COVID-19.

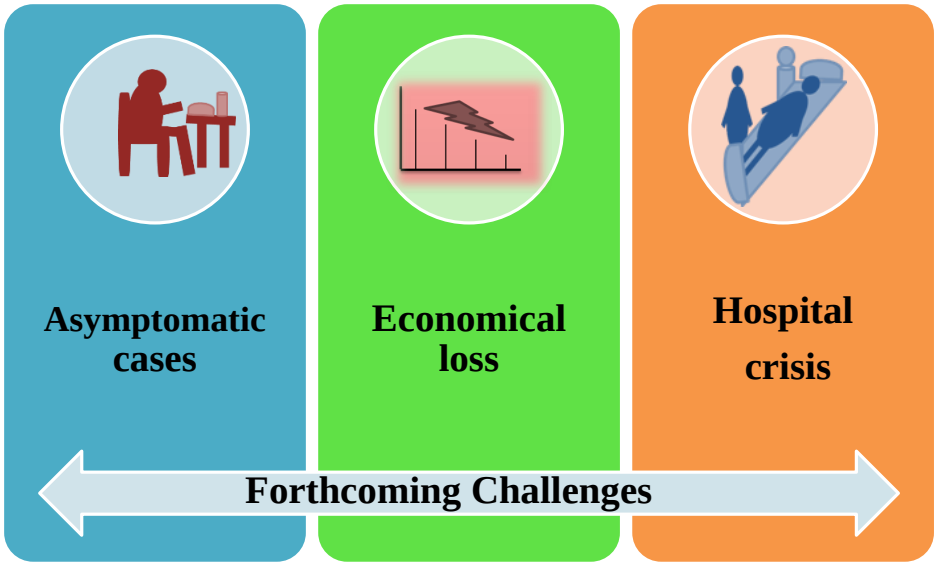

Fig. (1). Forthcoming challenges against COVID-19.

Globally, the main challenge is the aggressive diagnosis test of COVID-19 for early detection and prevention. Therefore, some reliable methods used to facilitate and speed the diagnosis of infection include serological test and RT-PCR test. However, mostly in developing countries, the problem is the limited access to these diagnostic assays in some regions. A successful diagnosis of COVID-19 is strictly bound with tracing of the positive case, especially in developing countries that have stumpy medical facilities [6]. Consequently, the exact number of people disease-ridden shows mild to moderate symptoms that need to be diagnosed early to prevent further spread. However, sometimes asymptomatic also able to transfer the infection to a new subject so, early detection must require to prevent further

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