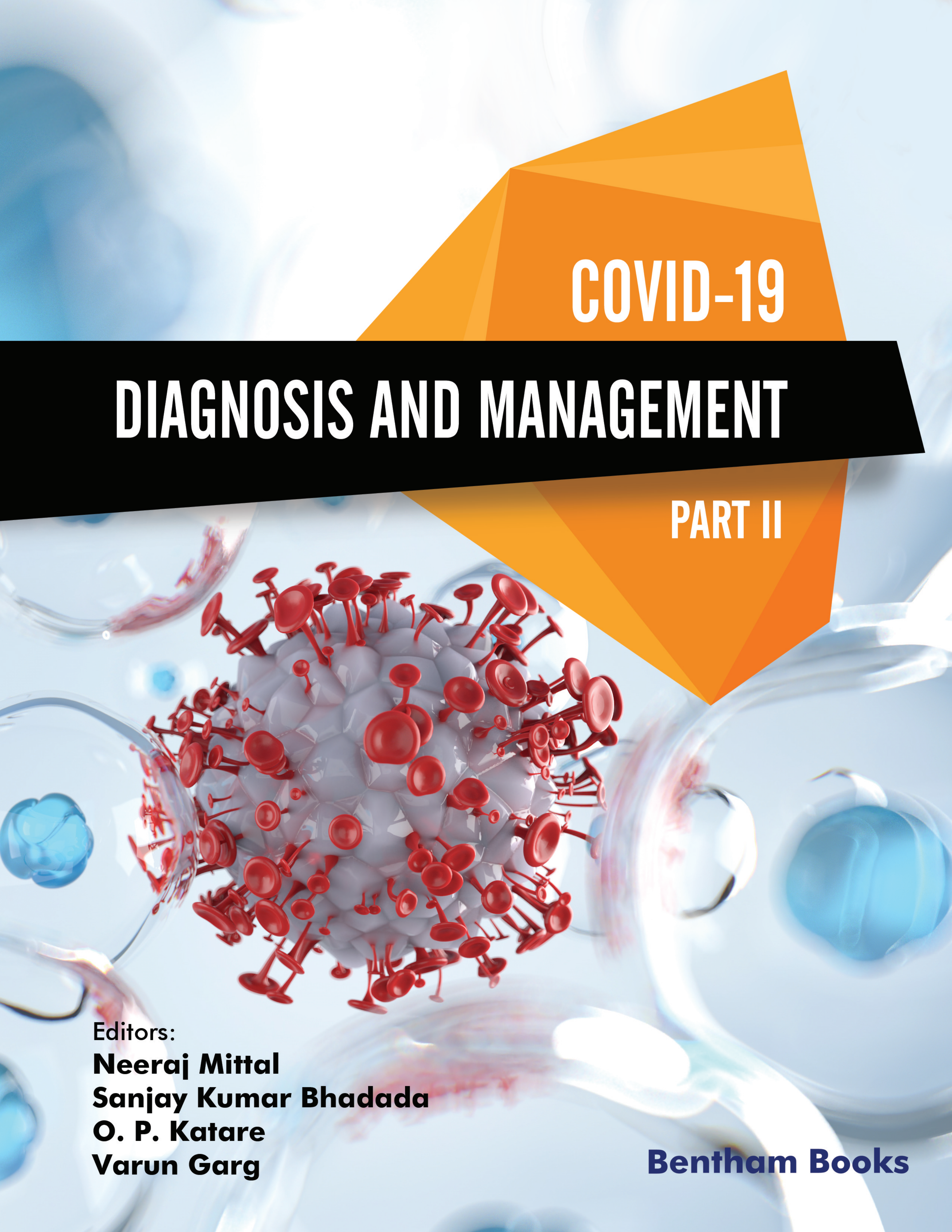

COVID-19

DIAGNOSIS AND MANAGEMENT

PART II

Editors:

Neeraj Mittal

Sanjay Kumar Bhadada

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Bentham Books

COVID-19: Diagnosis and Management-Part II

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FOREWORD

It is my proud privilege to introduce the book "Covid-19: Diagnosis and Management," which is authored by a group from PGIMER, Chandigarh. The timing of this monograph is very apt as it has been about 9 months since the start of the COVID-19 pandemic, and it is now that we are starting to unravel the various mechanisms of disease pathogenesis and treatment modalities for this viral infection which has infected 29 million people, out of which about 1 million have died globally.

It has been the need of the hour to come up with a treatment for this pandemic disease. Moreover, it is of utmost importance that all the information related to COVID -19 should be compiled in one place, a goal which this book will fulfill.

Though the tests for diagnosis of the infection have been developed in the start of the pandemic, there are still some issues in diagnosis, including the sensitivity of the best test available, *i.e.*, Real-Time Polymerase Chain Reaction.

The book is very well organized and has been divided into two parts; each part is comprised of 6 chapters and covers all the aspects of COVID-19 from the history to the treatment of the disease. Based on the best scientific studies available, the editors and authors have used their vast professional experience to discuss the all clinical aspects of COVID-19, including clinical presentation to diagnosis in the first part and treatment of COVID-19 in the second part, and I am very sure that this compendium will become the benchmark to refer to for any information required on COVID-19.

Whenever we write books, we must have in our minds, as clearly as possible, the affirmation of Carlyle Guerra de Macedo, who was the Director of Pan American Health Organization, relative to the responsibility of what is being published: "It must be remembered that behind each table, every report or material examined, there are lives, there are people, there is suffering, waiting for our efforts and human solidarity." Both the parts of the book are very well organized, and the readers will get a mine of information available to date on COVID-19 in one place, and it would be helpful to both the clinicians and the lab professionals for day-to-day guidance in various matters. The monograph is comprehensive but is written in a lucid manner that is easy to grasp, and even complex topics are made simple for understanding.

I am also sure that as the knowledge of the virus evolves further, the authors will certainly keep updating the work from time to time, further adding to the importance of the book. I would like to congratulate the editors/authors for this tremendous effort, and I am very sure that this book will surely be of use to readers around the world and help them in the diagnosis and management of patients with COVID-19 and will also go a long way in the efforts to help fight the pandemic, which is being faced by the humanity now.

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PREFACE

The coronavirus disease 2019 (COVID-19) outbreak has spread throughout the globe and declared as a pandemic by the World Health Organization (WHO) on 11th March, 2020. Till date on 1st September 2020, there are more than 25,327,098 confirmed cases of COVID-19 worldwide and around 848,255 deaths have been reported. The clinicians and scientists across the globe need all the information on this pandemic disease on one platform. We have already discussed history, epidemiology, and diagnosis in part I of this book. Part II of the book "COVID-19: Diagnosis and Management" is a concise and visual reference for this viral disease. It will provide comprehensive knowledge that will cover all the aspects related to the prevention and treatment methodology of this communicable disease COVID-19.

Key Features:

1. Chapter vise description and segregation of all the areas of management of COVID-19.
2. Six chapters cover prevention and treatment aspects of COVID-19.
3. Multiple tables and figures summarize and highlight important points.
4. Covering all the aspects of COVID-19 making this a perfect textbook for Virologist and medical students.
5. A summary of the current standards for the evaluation and clinical management of COVID-19.
6. A detailed list of references, abbreviations and symbols.

This book is an essential reference for practicing and training virologists, pulmologists, medical students, scientists working in various research labs, pharmaceutical and biotechnology industries on COVID-19.

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CHAPTER 1

Prevention of COVID-19: Facts to Overcome the Myths

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Abstract: The entire world has slowed down since the outbreak of a highly contagious virus, *i.e.*, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Extensive efforts are being made to reduce disease transmission, optimize the management strategy to reduce deaths and to come up with a vaccine as a preventive measure. Though several scientists across the globe are working tirelessly for developing an effective vaccine, it may still take several months to launch it successfully in the market. The behavioural interventions like maintenance of physical distancing (at least one meter), hand hygiene and cough etiquette, and use of personal protective equipment (PPE) are the currently available effective strategies to break the chain of disease transmission. All these interventions have been implemented at the population and individual level with or without linking with regulations. Based on the risk of exposure, provision and use of appropriate PPE is the need of the hour. The healthcare professionals working in COVID-19 areas have been recommended to use full PPE, which includes gloves, N-95 face masks, face shields, goggles, full-body gowns, and shoe covers. The general population has been asked to use homemade or triple-layered surgical masks in addition to the maintenance of physical distancing and hand hygiene. There are other additional strategies or measures which may or may not prevent the COVID-19 transmission. This chapter attempts to clarify the important and effective measures for the prevention of COVID-19 at the individual and community levels. It also tried to demystify the myths related to COVID-19.

Keywords: COVID-19, Diet, Disinfection, Face mask, Face shield, Filtering facepiece, Gloves, Hand hygiene, Home quarantine, Hydroxychloroquine, Institutional quarantine, N95 mask, Pandemic, Personal protective equipment, Physical distancing, Prevention, Sanitization, Screening, Transmission, Travel.

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INTRODUCTION

As it has been well-said, “Prevention is better than cure”, the same applies to the pandemic situation of COVID-19 as the causative virus is novel, and there is no specific treatment available. In this situation, only the preventive measures applicable to the community and individual level will help control the spread of infection and its impact. There are several preventive measures, specifically behavioural interventions like use of face masks or personal protective equipment, maintaining hand hygiene and physical distancing, practicing cough etiquette and others to contain the spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which have been discussed throughout this chapter (World Health Organization, 2020c). A thorough understanding of existing evidence on the mode of transmission of the infection is important to practice the preventive measures further.

The modes of transmission of coronavirus can be broadly categorized into two types. Direct transmission is characterized by close and direct contact of a healthy person with asymptomatic (less likely) or symptomatic COVID-19 patient, especially when a healthy individual comes into close contact (up to 2 meters) and has been exposed to the respiratory droplets (>5-10μm diameter) produced by sneezing, coughing, talking and other activities (Bai *et al.*, 2020). Indirect transmission of infection happens through contact with fomites. It is generated during sneezing and coughing, which may deposit on clothes and even surfaces or objects, making it viable for transmission (Guo *et al.*, 2020). However, the evidence on airborne transmission (through droplet nuclei-diameter <5μm) and transmission through the faeco-oral route is extremely limited. Though mother-to-child transmission is highly unlikely, the newborn baby is equally at risk of acquiring the disease like others for the person-to-person transmission through respiratory droplets or through contact with fomites (Sohrabi *et al.*, 2020; World Health Organization, 2020b). Table **1** summarizes the myths and facts related to the transmission of COVID-19 (Fong, 2020).

Table 1. COVID-19 transmission associated myths and facts.

Sr. No.	Myth	Fact
1	Coronavirus cannot be transmitted in extreme weathers like hot and humid or cold/freezing temperatures	There is no evidence till date that supports these theories and has been denied by WHO as well. The virus can stay viable even at significantly high temperatures, and this fact is supported by the increasing number of cases in India.
2	The novel coronavirus can spread through mosquitoes and houseflies	No. It is not. It is spread by respiratory droplets and through contacts.

(Table 1) cont.....

Sr. No.	Myth	Fact
3	Only people with symptoms of this disease can spread it	Though transmission by an asymptomatic person is unlikely and no robust evidence available, it is possible.
4	Tobacco smoking prevents from corona infection	No. Actually, it may increase the risk of severe disease due to lowering lung function and hence increased mortality.
5	Being able to hold the breath for more than 10 seconds is a sign of the absence of virus	As more than 80% of patients present without any symptoms or with mild disease, they can hold the breath even during the acute stage.
6	Use of hand dryers can kill the virus	Hand dryers are not an effective disinfectant method against coronavirus. Alcohol-based sanitizers or hand wash using soap and water is an effective method.

MEASURES TO PREVENT THE SPREAD, ASSOCIATED MYTHS AND FACTS

The preventive measures ranged from using a simple face mask to using a full set (from head to toe) of personal protective equipment. Similarly, the preventive measures work together and effectively prevent the transmission of the disease like the use of face mask, physical distancing, maintenance of hand hygiene and others. Further, most of the measures are related to changing the behaviour and practice, some of which are linked with regulations.

Personal Protective Equipment (PPE)

The PPE can act as a physical barrier, or it is something that protects a person from any lethal biological agent when used properly (World Health Organization, 2020d).

PPE can be divided into various components, such as:

1. Head Cap/cover
2. Face Shield
3. Mask
4. Goggles
5. Gloves
6. Shoe Cover
7. Gowns or Coveralls

All the above-mentioned components together make a complete PPE, and a brief explanation on them, rationale of their use and the standards thereof are discussed below:

CHAPTER 2

Current Treatment Methods for Coronavirus Disease-19

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Abstract: The coronavirus disease (COVID-19) pandemic outbreak has created health havoc all over the world. Till now, no definite treatment has been found to combat the COVID-19 outbreak, probably due to a poor understanding of the molecular mechanism of this infection. As it's a health devastating situation, so due to lack of proper time for research, clinicians all over the world are exploring the already approved drug such as lopinavir, ritonavir, chloroquine (CQ), hydroxychloroquine (HCQ), azithromycin (AZ), remdesivir, favipiravir, ribavirin, nitozoxanide, interferon-α (IFN), arbidol, corticosteroids, ivermectin, teicoplanin, herbal drugs, *etc.* for anti-viral activity. Previous studies suggest that these drugs act by different mechanisms such as prevention of entry and fusion of the virus with host cell by blocking angiotensin-converting enzyme-2 (ACE-2) receptor and increasing endosomal pH respectively, inhibition of RNA polymerase and protease enzyme, inhibition of inflammatory pathway by blocking toll-like receptors (TLR's), inhibition of RNA synthesis, interference of glycosylation of cellular receptor, suppression of immune response, *etc.* Besides these drugs, few humanized monoclonal antibodies such as tocilizumab and sarilumab are also shown to be effective against COVID-19 by blocking interleukin-6 (IL-6) receptors. In addition to these drugs, convalescent plasma therapy is also being used to treat COVID-19 patients. Focus is on the development of a vaccine for COVID-19 at the earliest and indeed, many vaccines are in various stages of the development process, with some under clinical trials. This review gives an exhaustive view of current therapeutic strategies for the management of COVID-19.

Keywords: ACE-2, Arbidol, Azithromycin, COVID-19, Corticosteroids, Favipiravir, Hydroxychloroquine, IL-6, Immune response, Interferon-α, Ivermectin, Lopinavir, Monoclonal antibodies, Plasma therapy, Protease, Remdesivir, Ribavirin, Ritonavir, RNA polymerase, TLR's, Tocilizumab.

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INTRODUCTION

The coronavirus disease (COVID-19), also referred as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been the major health outbreak nowadays. This virus was firstly detected from Wuhan city of China in December, 2019, and now it has been spread worldwide (more than 190 countries) (Wang *et al.*, 2020). Till the end of May 2020, over 6 million human beings are reported to be affected and nearly half a million deaths have been reported due to COVID-19. Health machinery all over the world is trying its very best to combat this pandemic and facing a real challenge to tide over this crisis. Till today, no definite treatment has been found to combat this COVID-19 outbreak. Besides probationary drug therapy, some preventive, supportive, and precautionary measures such as self-isolation, social distancing, avoid unnecessary travel and crowded places are being advised and exercised to prevent the spread of this devastating infection (Chen *et al.*, 2020). Due to lack of time and a health emergency, clinicians are exploring the already approved drug for anti-viral activity (Savarino *et al.*, 2006; Rolain *et al.*, 2007; Mullard, 2012; Yan *et al.*, 2013; Agostini *et al.*, 2018; Bleibtreu *et al.*, 2018; Colson *et al.*, 2020; Cao *et al.*, 2020). In the wake of this, a number of drugs such as lopinavir, ritonavir (Cao *et al.*, 2020), chloroquine (CQ), hydroxychloroquine (HCQ) (Savarino *et al.*, 2006; Yan *et al.*, 2013), remdesivir (Agostini *et al.*, 2018), favipiravir, ribavirin, interferons (IFN's), corticosteroids, oseltamivir (Bleibtreu *et al.*, 2018), *etc.* have been tested on COVID-19 infected patients and are in current practice but with variable success. Critical insight into various treatment methods currently being employed to manage COVID-19 infection is being given in this review.

OVERVIEW OF VARIOUS TREATMENT STRATEGIES FOR COVID-19

Hydroxychloroquine

Cinchona bark and its derived constituents are considered as the primary treatment for malaria (Ruiz-Irastorza and Khamashta, 2008). CQ, a 9-aminoquinoline, has been used as the most effective anti-malarial compound (Wellems and Plowe, 2001). HCQ (7-Chloro-4-[4-(N-ethyl-Nb-hydroxy-methylamino)-1-methylbutylamino]quinoline sulfate) is a hydroxyl analogue of CQ that is a more safe and efficacious molecule (Sperber *et al.*, 1995). HCQ is a widely used clinical agent not only in the treatment of malaria but also for many other disorders such as fungal infections (Byrd and Horwitz, 1991; Henriet *et al.*, 2013), rheumatoid arthritis (RA) (Rainsford *et al.*, 2015), systemic lupus erythematosus (SLE) (Jessop *et al.*, 2001; Rainsford *et al.*, 2015), sjogran's syndrome (Oxholm *et al.*, 1998) and polymorphic light eruption (PLE) (Pareek *et al.*, 2008). In addition to the above disorders, HCQ is also demonstrated to possess anti-viral activity and has been used clinically for the treatment of several viral infections such as human immunodeficiency virus-1 (HIV-1) (Chiang *et al.*, 1996), Zika virus (ZIKV) (Kumar *et al.*, 2018), dengue virus (DENV) (Wang *et al.*, 2014) and severe acute respiratory syndrome coronavirus (SARS-Co-V) (Vincent *et al.*, 2005). HCQ has efficient absorption after oral administration with peak plasma concentration reaching after 2-3.5 hours and it has an elimination half-life around 22-45 days (Tett *et al.*, 1989; Lim *et al.*, 2009).

HCQ in Treatment of COVID-19

HCQ has become a molecule of the moment because of its utility in managing COVID-19 infection. Many *in-vitro* and controlled and uncontrolled clinical trials have substantiated the activity of HCQ against COVID-19 (Gautret *et al.*, 2020; Liu *et al.*, 2020; Yao *et al.*, 2020). These *in-vitro* reports are further supported by many clinical trial studies carried out, and being conducted in different countries such as China, U.S, Europe, *etc.* (Gao and Yang, 2020; NCT04261517; NCT04307693). Therefore, HCQ has seen variable success in these clinical trials. In a non-randomized, open-label clinical trial conducted out in France, 20 patients of COVID-19 were administered with HCQ at the dose of 200 mg three times daily (TID) and were compared with another group of patients who received supportive care. It was concluded that all patients well tolerated the HCQ and showed fast clearance of virus (Gautret *et al.*, 2020). Moreover, another study conducted in China reported that HCQ at the dose of 400 mg daily did not show any clinical benefits in mild COVID-19 patients (Chen *et al.*, 2020). Another parallel study from China conducted on more than 100 patients of COVID-19 gave evidence of less severe pneumonia, improvement in lung imaging and decreased disease duration in comparison to control group patients after receiving HCQ (Gao and Yang, 2020) and it was also documented that the treatment was safe. This study gave confidence to the experts in China to recommend HCQ at the dose of 500 mg twice daily for 10 days to mild, moderate, and severe patients of COVID-19 (Zhonghua *et al.*, 2020).

Probable Mechanism of HCQ in Treatment of COVID-19

It is being hypothesized that HCQ acts by inhibiting the replication of viral nucleic acid, glycosylation of viral proteins, assembly and transport of virus and release of virus molecule to achieve its anti-viral activity (Fox, 1993; Wang *et al.*, 2015; Kumar *et al.*, 2018) (Fig. **1**). It is suggested that HCQ has an immuno-modulatory effect, which further helps in decreasing the elevated level of cytokines, interleukin-6 (IL-6), and IL-10, which are primary contributors to multi-organ failure and death in COVID-19 patients (Chen *et al.*, 2020; Huang *et al.*, 2020). It is also being considered from the previous history of HCQ for

CHAPTER 3

COVID-19 and Mortality

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Abstract: The novel coronavirus disease (COVID-19) has scourged the world ever since its outbreak in December 2019 in Wuhan, China. The disease tends to be asymptomatic or mild in nearly 80% of the patients. However, around 5% of the patients tend to have critical disease complicated by acute respiratory distress syndrome (ARDS), shock and multiple organ failure. Mortality in COVID-19, as represented by the case-fatality rate (CFR), is around 6% (as of June 4, 2020). The CFR of COVID-19 is lower as compared to other coronavirus-related diseases like the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS), however, it is likely to increase as we reach the end of the pandemic. The CFR also varies widely from one nation to another with the maximum mortality being hitherto reported from the European nations and the least from Singapore, Cambodia, Vietnam and Iceland. The common causes of death in COVID-19 include respiratory failure, consequently leading to ARDS, pulmonary thromboembolism, shock and multiple organ failure. Advancing age and presence of comorbid illness are consistently associated with an increased risk of death, while certain biochemical and hematological parameters, notably C-reactive protein, IL-6, cardiac troponin, D-dimer and absolute count can also help predict mortality in patients with COVID-19.

Keywords: ACE2, ARDS, Case-fatality rate, Comorbidities, COVID-19, Cytokine storm, D-dimer, Death, Diabetes mellitus, Hypertension, IL-6, Lymphopenia, Mortality, Mortality rate, Novel coronavirus disease, Old age, SARS-CoV-2, Shock, Thromboembolism, Troponin.

INTRODUCTION

An unprecedented outbreak of 'pneumonia of unknown cause' emerged in the Wuhan City of China in December 2019 (Pneumonia of unknown cause – China, 2020). The patients presented with clinical symptoms of fever, dry cough, dyspnea, and bilateral lung infiltrates on imaging. Cases were claimed to be all

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linked to the Wuhan's Seafood Wholesale Market, which trades in fish and a wide variety of live animal species, including poultry, bats, rats, marmots, and snakes. The causative pathogen was identified from throat swab samples collected from the patients and was subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was named novel coronavirus disease (COVID-19) by the World Health Organization (WHO). With the increase in the number of cases outside China, the WHO declared the outbreak of COVID-19 to be a Public Health Emergency of International Concern, posing a high risk to countries with vulnerable health systems on January 30, 2020. Subsequently, with the emergence of new epicenters in Italy and Iran, COVID-19 was declared a pandemic on March 11, 2020.

Ever since its outbreak, COVID-19 has scourged the world, affecting over 6.2 million people, inflicting more than 379000 casualties worldwide (Coronavirus disease (COVID-19) Situation Report – 135, 2020). Hitherto, the maximum number of cases has been reported from the United States of America, Brazil, Russia, the United Kingdom, Spain, Italy, India, Germany, Peru, Turkey, Iran and France (Coronavirus (COVID-19), 2020). The inherent ability of SARS-CoV-2 to withstand extremes of the ambient environment and its remarkable stability on inanimate objects and surfaces make it an ideal pathogen for human-to-human transmission. The basic reproductive number (R_0) of COVID-19, defined as the average number of secondary cases attributable to infection by an index case after that case is introduced into a susceptible population, is high, ranging from 1.5 to 6.68 with a mean of 3.28 (Liu *et al.,* 2020). The high R_0 of SARS-CoV-2 has accounted for the rapid increase in the number of COVID-19 cases worldwide. In addition, there have been instances of super-spreader events, in which an individual, who may or not be symptomatic, infects a large number of susceptible subjects (Coronavirus disease 2019 (COVID-19) Situation Report – 24, 2020.; Coronavirus disease 2019 (COVID-19) Situation Report – 36, 2020). In fact, the outbreak of COVID-19 in Wuhan might have been a super-spreader event as it had coincided with one of the world's largest mass gathering, the Chinese Spring Festival (Ebrahim and Memish, 2020).

Despite being highly contagious, more than 80% of patients with COVID-19 are either asymptomatic (no pneumonia) or have mild symptoms (mild pneumonia). Only 14% of patients develop the severe disease; the rest 5% develop critical disease manifesting as respiratory failure, septic shock, and/or multiple organ dysfunction or failure (Wu and McGoogan, 2020). Case-fatality rates in COVID-19 have been highly variable, ranging from as low as 0.5% to as high as 21.8% (Mortality Risk of COVID-19, 2020). Nevertheless, advancing age and the presence of underlying co-morbidities have been consistently associated with increased mortality in COVID-19. In addition, certain biochemical parameters have emerged as potential predictors of mortality in COVID-19.

Herein, we have discussed in detail the multiple aspects of mortality in relation to COVID-19.

REPRESENTING MORTALITY – MORTALITY RATE *VS.* CASE-FATALITY RATE

Often the terms mortality rate and case-fatality rates are used interchangeably. Although both the parameters are used to define death rates, the two are not synonymous. According to the *Dictionary of Epidemiology*, the mortality rate is defined as "an estimate of the portion of a population that dies during a specified period". Going by the definition, the mortality rate should be ideally expressed as the number of deaths occurring per 100000 population per year, rather than representing the figure as a percentage. On the other hand, the case-fatality rate (CFR) is defined as "the proportion of cases of a specified condition that are fatal within a specified time" (Spychalski *et al.,* 2020). Accordingly, most of the estimates of death expressed as a percentage are case-fatality rates rather than mortality rates. We have referred to CFR throughout the subsequent discussion unless otherwise specified.

FALLACIES IN ESTIMATING MORTALITY USING CASE-FATALITY RATE

Case-fatality rates amid an ongoing pandemic should be interpreted with caution. The CFR is affected by the total number of cases (the denominator) as much as it is affected by the actual number of deaths (the numerator). For example, in countries where massive population screening has been undertaken, as in Switzerland and South Korea, case-fatality rates are less than 1%, as the denominator includes a large number of mild/asymptomatic cases. However, in countries where only symptomatic patients or those requiring hospital admissions are being screened, as in Italy and Spain, case-fatality rates have exceeded 5%, because the denominator is much smaller (Vincent and Taccone, 2020). Besides, the CFR might be over or underestimated based on how a 'case' is defined. During an ongoing epidemic, cases might be defined either as total cases (every confirmed case) or as closed cases (only those who have recovered or died). Hence, the denominator for calculating CFR might be either of these numbers. In the initial phase of an epidemic, the number of closed cases is relatively small, and so the CFR calculated per closed cases is an overestimate. By contrast, when the CFR is calculated per total cases, the whole calculation becomes an underestimate. As an example, early in the course of COVID-19, even before it was declared a pandemic, the WHO had opined on March 3, 2020, that the global COVID-19 CFR was 3.4% (WHO Director-General's opening remarks at the

CHAPTER 4

Long Term Complications of COVID-19

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Abstract: Coronavirus disease 2019 (COVID-19) is an acute respiratory illness. It is caused by a novel coronavirus (SARS-CoV-2). It has gained widespread recognition after it originated from China. The World Health Organisation (WHO) declared the outbreak of COVID-19 as an international public health emergency. Patients of COVID-19 develop long-time complications along with severe health problems as it majorly affects the respiratory system, utilizing angiotensin-converting enzyme 2. Characteristic symptoms include fever, cough, and dyspnea, although some patients may be asymptomatic. People need extensive care to be protected from anxiety and depression. This outbreak harmed various organ systems and led to the development of long-term complications such as respiratory failure, pneumonia, pancreatic complications, cardiac injury, secondary infections, renal disorders, disseminated intravascular coagulation, and rhabdomyolysis. Individuals with comorbidities are at higher risk of illness and mortality. The risk is also increasing in older people, especially people the age of 60-80 years or more. The most prevalent comorbidities are asthma, neurologic disorders, diabetes, obesity, cardiovascular disease, and malignancy/hematologic conditions. As there is no specific treatment available so far, therefore complications of this disease are also increased by the use of non-specific drugs. The recovery of these patients is another major challenge for health care professionals. So in this chapter, we will discuss long-term complications associated with COVID-19.

Keywords: Cardiovascular diseases, Coronavirus, COVID-19, Diabetes, Mortality, Neurological effect, Pandemic, Renal effect, Respiratory effect, Rheumatoid arthritis.

INTRODUCTION

The latest coronavirus 2019 (2019-nCoV) or SARS-COV-2, a respiratory synd-

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rome, has rapidly spread from the Wuhan Town of Hubei, China, to the rest of the world. Coronavirus 2019 (COVID-19) is a consequence of severe acute respiratory syndrome that is now a significant concern for global public safety and local communities (Li *et al.*, 2020b). More importantly, following considerable initiatives and a rising number of remedies in China, the disease has now started to spread from China to Europe, North America, and other Asian countries (Wu and McGoogan, 2020). Coronavirus is a positive-sense RNA virus with spike-like projections having a diameter of about 60-140 nm. Under the electron microscope, it shows its crown-like appearance; thus, the term coronavirus has been used for it. There are four different types of coronaviruses (HKU1, NL63, 229E, and OC43). They are responsible for causing mild respiratory diseases in humans (Singhal, 2020). If an individual is suffering from COVID-19, their clinical symptoms range from asymptomatic disease to respiratory failure and finally leading to multiple organ dysfunction. Such kind of developed complication leads to the death of patients. The commonest health symptoms in COVID-19 include fever, cough, headache, sore throat, myalgia, fatigue, and respiratory illness. Conjunctivitis is also reported in some of the patients of COVID-19. Therefore it is difficult to distinguish this from other respiratory infections (Lima, 2020).

By the completion of the first week after the reports of the spread of COVID-19, cases of pneumonia, respiratory failure, and death were reported. This breakthrough is related to the significant increase in inflammatory cytokines like IL2, IL7, IL10, and TNFα. A person of any age group is susceptible to this disease. Symptomatic patients of COVID-19 release their large droplets through cough and sneezing. These incidences cause the spreading of infection of COVID-19. This spread of infection may also arise from asymptomatic individuals even before the occurrence of symptoms. In contrast with the mouth, higher viral loads have been observed in the nasal cavity. Moreover, patients can remain contagious as long as the virus survives in them, and also after they are fully recovered (Wu *et al.*, 2020a, Singhal, 2020). The development of such a condition of infection is due to the passing of the virus through the mucous membranes. It enters the human body through nasal and larynx mucosa. After that, it enters into the lungs through the respiratory tract. As a result of this, fever and cough are the most common symptoms of infection to appear. Further, it causes viremia when it invades into peripheral blood through the lungs. Then the virus attacks the targeting organs that express Angiotensin-converting enzyme 2 (ACE2), such as the lungs, heart, renal, gastrointestinal tract. The fecal samples have also been found to have evidence of SARS-CoV-2. The reason behind this detection is due to the entry of this virus takes place through the lung to blood and then it propagates from the blood to the intestines. During the process of infection, the count of white blood cells is normally or slightly less in peripheral blood at an early stage only. But as time progresses the lymphopenia is observed in patients (Cheng *et al.,* 2020a). The critical stage is appearing in this disease as a reduction of B lymphocyte occurs in the early stage of this disease only, which may affect the production of antibodies. It is also noticed that the patients having a severe stage of the COVID-19 reduction of lymphocytes significantly takes place (Cheng *et al.,* 2020a). The increased level of neutrophils, D-Dimer, blood urea nitrogen, and creatinine was reported in non-survivors than the survivors. Based on these recently reported facts and assumptions, the clinical stages can be divided as follows:

a. The viremia stage.
b. The acute stage (pneumonia phase) and
c. The recovery stage (Guan *et al.*, 2020, Wang *et al.*, 2020a, Letko *et al.*, 2020).

The coronavirus disease pandemic is causing significant morbidity and mortality in patients having a long history of any diseases associated with primary disease. Older age, diabetes mellitus, cancer, chronic kidney disease, rheumatoid arthritis, hypertension, and obesity greatly raise the likelihood of hospitalization and mortality in patients with COVID-19 (Guo *et al.*, 2020a). In this context, we explore the long-term complications of COVID-19 in patients suffering from various diseases.

LONG TERM COMPLICATIONS OF COVID-19

The meaning of the long history of diseases is chronic complications and it can be defined as the clinical state of suffering that tends to arise over the years and persists for decades. In this, patients used to suffer from not only the various complications of primary diseases but also secondary or multiple diseased states. Even though a large number of people are impacted by the COVID-19 pandemic, the most vulnerable are the aged, under-represented minorities, and underlying diseases. The increasing consumption of an unhealthy diet with excessive amounts of saturated fats, carbohydrates, and sugar persuade the pervasiveness of obesity and type 2 kind of diabetes and may raise the likelihood of seriousness of COVID-19 disease and its mortality (Butler and Barrientos, 2020). A healthy diet is very important for the development of immunity. Immunity and lifestyle (daily habit of food intake) are related to each other. So if the person taking an unhealthy diet or careless about the daily nutritious diet intake invites stimulation of the innate immune response and impairment of adaptive immunity which is inducing persistent inflammation, and finally brings disruption of the host defense system. Besides, the long-standing impact of peripheral inflammation induced by COVID-19 contributes to chronic medical disorders such as neurodegenerative disorder and dementia. These conditions are developed possibly through

CHAPTER 5

Vaccine Development

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Abstract: The current COVID-19 pandemic is a wake-up call pointing towards the vulnerability of humankind as it has outstretched its arms to almost all the continents, sparing few socially isolated ones. The highly contagious nature, ultra-stable genetic makeup, novel modifications in open reading frame (ORF) region, air-born route of transmission, and ability to cross the species barrier prove the potential of COVID-19 to elicit the global pandemic situation. In current times, when even known antibiotics for combating several diseases are being rendered inefficacious owing to the rising multidrug resistance among pathogenic strains, the panacea to a wide array of diseases can be vaccination. A prominent characteristic for COVID-19 vaccine development is that numerous technologies from lipid nanoparticle (LNP)-encapsulation, dendritic cells (DCs)-based vaccines, antigen-presenting cells (artificial-APCs)-based vaccines, and DNA plasmid-based platforms to viral vector approaches are being evaluated for the cause. Certain vaccine development technologies may be better suited for some parts of the global population, while others may prove to be more efficacious for the other population subtypes. This may not only be arising due to geographical or ethnic distinctions, but also physiological differences such as the presence of comorbidities, immune profile of subjects, *etc.* In this chapter, we attempt to bring forth the various approaches or molecular platforms that have been taken up or proposed for the development of a vaccine against coronavirus disease. We also attempt to elaborate on the pros and cons associated with each of the approaches that may be feasible due to the distinctions in the various population subtypes.

Keywords: Air-borne transmission, Animal model, APCs-based vaccines, Artificial-APCs, Comorbidities, COVID-19, DCs-based vaccines, DNA plasmid-based platforms, Genetic makeup multidrug resistance, Global population, Immune profile, Lipid nanoparticle (LNP), Molecular platforms, Novel modifications, Pathogenic strains, Physiological differences, Population subtypes, Vaccine development, Viral vector approaches.

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COVID-19: VACCINE DEVELOPMENT

Over the past decade, vaccine technology has undergone immense evolution, and different approaches for the development of vaccines against viruses and other pathogens have emerged. The advancement has enabled researchers to develop a wide range of vaccine candidates such as nucleic acid-based (DNA/RNA) vaccines, recombinant protein-based vaccines, and viral-vectored vaccines, *etc*. The rapid revelation of the genetic map of the SARS-CoV-2 viral genome has opened avenues facilitating several vaccine development programs against COVID-19 (Liu *et al.*, 2017). As of the current scenario, there is no antiviral drug available as a frontline treatment for the disease. To conquer the threat of COVID-19, urgent therapeutic intervention is the need of the hour, and therefore several strategies for vaccine development, besides drug development, have been initiated (Taghizadeh-Hesary and Akbari, 2020). As a result of these, there are currently 115 potential vaccine candidates across the globe, 78 of which are established as active projects; 5 among those candidates have already successfully crossed the pre-clinical stages (Grifoni *et al.*, 2020).

It is a remarkable feature of research & development for the COVID-19 vaccine that a wide assortment of platforms is being tried out. As mentioned earlier, platforms including nucleic acid-based vaccines, recombinant proteins, live attenuated virus, as well as inactivated virus-based approaches, alongside viral peptides, virus-like particles (VLPs), and replicating/non-replicating viral vectors are being explored for the development of SARS-CoV-2 vaccine. It is advantageous that several approaches have been taken up, especially concerning the fact that certain immunization technologies may be efficient for a specific group of population. This specific effectiveness relates not only in terms of age, ethnic, or epigenetic differences but also correlates to the physiological variances such as the presence of certain comorbidities (Grifoni *et al.*, 2020). The extensive study on the SARS-CoV-2 virus and its genome has revealed potential targets for vaccines and drug interventions. Bioinformatics and computational tools have a significant role to play in recognizing the most competent targets. A large number of databases have been created for easy and correct identification of potential vaccine targets (Taghizadeh-Hesary and Akbari, 2020). The characterization of the SARS-CoV-2 spike glycoprotein has enabled the researchers to identify precise immunogenic epitopes that can be taken into account for vaccine development. Their extensive analysis pointed out 13 and 3 epitopes for MHC-I & II respectively on the spike glycoprotein of the virus that can be incorporated in the formulation of a multi-epitopic peptide vaccine. Further, these candidate epitopes have been assessed for their effective immunogenicity through molecular docking with TLR-5; However, *in vitro* and *in vivo* validations are required to confirm the potential of this vaccine candidate. The fact that the SARS-CoV-2 virus is proximally related to MERS and SARS viruses which has allowed researchers to utilize structure-function comparisons to hasten the process of recognizing potential vaccine candidates (Taghizadeh-Hesary and Akbari, 2020).

Nevertheless, there are certain challenges associated with vaccine development. After the identification and *in silico* validation of a vaccine candidate, it is taken forward for a formulation, which itself is a long process. In the first phase, it passes through the rigorous tests for the efficacy and safety in animal models. It is safe to consider the fact that developing suitable animal models for SARS-CoV-2 may be a challenge in itself, as the virus is known to not propagate in wild-type mice; Further, this virus only induces a mild form of the disease in transgenic animals that are engineered to express human ACE2 (Liu *et al.*, 2017). However, even in the absence of animal models, it is not entirely impossible to assess the vaccine candidate. Serum obtained from the immunized animals can be further validated through *in vitro* testing *via* neutralization assays. The remaining part of this tier is to gauge the vaccine candidate for its safety in animals in a manner acquiescent to the GLP (Good Laboratory Practices) guidelines and usually lasts for a minimum period of 6 months. This is followed by the production of vaccine compliant to current good manufacturing practice (cGMP) that assures the quality and safety of the vaccine. The second tier that includes the clinical phase I (small trials to evaluate safety on humans), phase II (aimed at establishing dosages and formulations to substantiate efficacy in humans), and phase III trials (both efficacy and safety of the vaccine candidate should be validated in a larger population). However, in certain unexpected conditions, such as during the pandemic of COVID-19, the guidelines may be flexible, and the process for approval may be accelerated with necessary precautions taken.

COVID-19 VACCINE DEVELOPMENT: MODULATING THE HOST IMMUNE SYSTEM

To understand the mechanisms of immunization that can facilitate the modulation of the host immune system in response to SARS-CoV-2, it is substantial that we apprehend the natural manifestations that the host system gradually adapts to modulate the response to the viral infection. The virus can successfully invade the cells which express the ACE2 and TMPRSS2 (transmembrane protease serine 2) surface receptors. Once the cells get infected, the viral genome undergoes active replication followed by cascade steps and releases the copies of the packaged virus from the infected cell. It is followed by pyroptosis, a mechanism through which cells release the damage-associated molecular patterns (DAMPs). These DAMPs are recognized by surrounding cells such as epithelial cells, endothelial cells, and alveolar macrophages, which in turn trigger a pro-inflammatory condition in the milieu by inducing the generation of cytokines and chemokines,

CHAPTER 6

The Future of COVID-19 Treatment

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Abstract: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or coronavirus disease or COVID-19 is a disease that has led to colossal mortality worldwide. The fast spread of this disease has caused havoc and panic among individuals, which has further worsened with the unavailability of vaccines or some proven drug regime. To date, only 12 new antiviral drugs have been approved by the FDA (8 against hepatitis C virus (2 in combinations for HIV). Thus, it becomes of utmost importance to identify drugs for new and re-emerging viruses, including the coronavirus. Considering the quest, we have put forth this book chapter to update readers about current repurposed and experimental drugs for this novel coronavirus. The viral lifecycle assisted in providing vital potential targets for drug therapy. The present chapter also deals with the existing mechanism of action of the drugs, their category, and clinical data reported.

Keywords: ACE2 inhibitors, Antiarrhythmic, Antibacterial, Anticancer, Anticoagulants, Antidiabetic, Antifungal, Anti-inflammatory, Antimalarial, Antioxidant, Antiparasitic, Antiprotozoal, Antiviral, Chelating agents, COVID-19, Drug repurposing, Natural products, Psychotropics, RAAS-ACE-ARBs inhibitors, SARS-CoV-2.

INTRODUCTION

Considering the COVID-19 pandemic, it becomes of utmost importance to identify drugs that possess potential and efficacy in treating COVID-19 disease (Mercorelli *et al.*, 2018, Cupertino *et al.*, 2020). The COVID-19 disease is notably marked with attacks at the lower respiratory system that leads to viral pneumonia along with affecting kidney, liver, heart, central nervous system, and gastrointestinal system leading to multiple organ failure responsible for high morbidity (Su *et al.*, 2016, Zhu *et al.*, 2020). Recently, drug target validation in

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SAR-CoV-2 has led to the identification of newer targets for therapeutic development (Mani *et al.*, 2019). To date, (June 4, 2020) 53 targets have been identified.

The important one includes non-structural proteins, spike proteins, membrane protein, nucleocapsid proteins, *etc.* The identified targets/proteins possess enzymatic activities and catalyze the virus-cell cycle by hijacking the host cells.

The virus division cycle (Fig. **1**) consists of six phases, which include attachment of virus with the host cell receptors, allowing its entry, followed by translation, replication, and release, and the subsequent damage resulting from the compromised immune system.

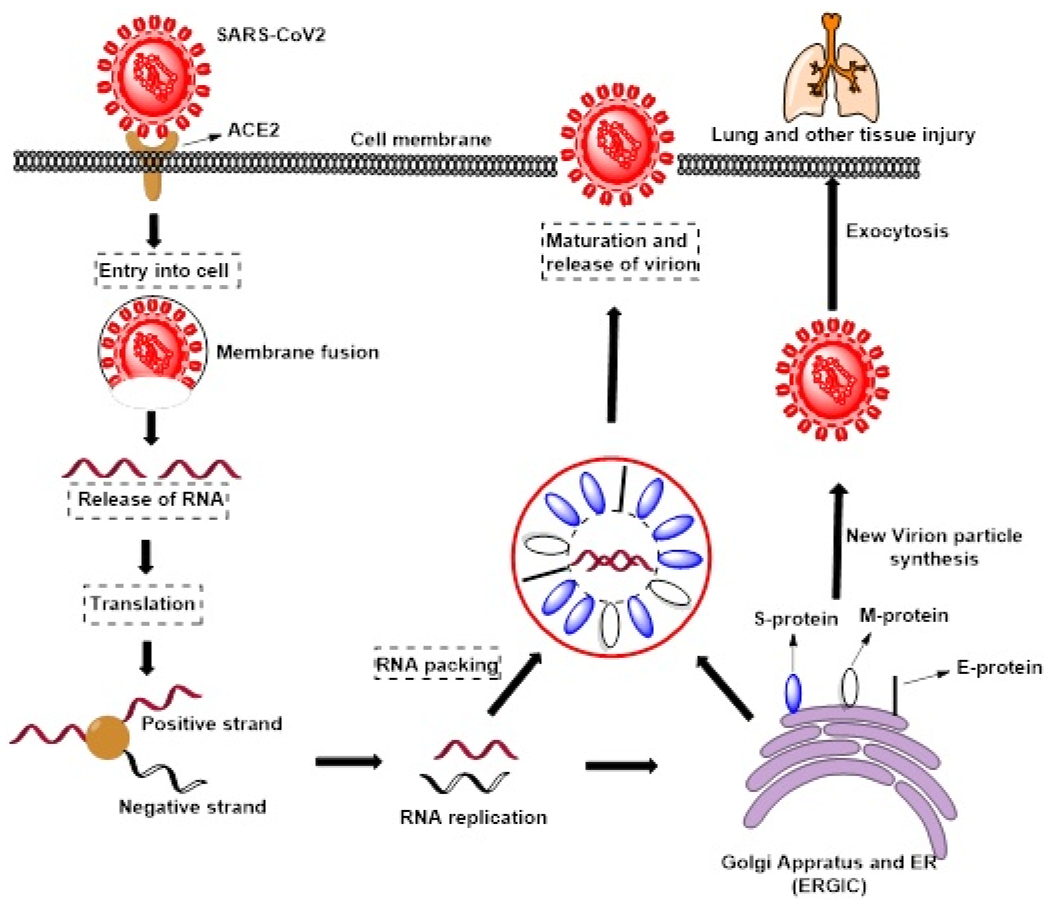

Fig. (1). SARS-CoV-2 life cycle in the host cell. The cycle consists of critical phases starting from the attachment of the virus with host cell receptors, endocytosis, proteolysis, translation, replication, maturation, and release of mature virions that ultimately are shredded, leading to subsequent damage of the organ system resulting from the compromised immune system.

Taking into account the reported interaction pattern of the virus with the host cell, many drugs have been repurposed so far. The drugs are currently under various clinical trials, and their efficacy and potential are still awaited. Drug repurposing characterizes a practical drug discovery approach from already known drugs (for different therapeutic use). It could minimize the time and decrease the cost associated with the *de novo* drug discovery (Zhou *et al.*, 2020b). This practice has been gaining popularity in recent years (Aubé, 2012). The approved drug requires regulatory approval for novel therapeutic applications which were already optimized for efficacy and safety in a particular disease (Chong *et al.*, 2007). The strategy used for drug repurposing involves identification of ligand for an indication of interest, drug assessment in preclinical models by mechanistic interpretation, efficacy evaluation in phase II clinical trials. There are various approaches used for drug repurposing, such as computational and experimental approaches. Computational approaches include molecular docking (Kitchen *et al.*, 2004), signature matching (Hieronymus *et al.*, 2006), pathway mapping(Smith *et al.*, 2012), genetic association (Sanseau *et al.*, 2012), novel data sources (Althouse *et al.*, 2015), and retrospective clinical analysis (Hurle *et al.*, 2013). Experimental approaches, such as phenotypic screening (Moffat *et al.*, 2017) and binding assays, are involved in the identification of relevant target interactions (Molina *et al.*, 2013). Some of the success stories of drug repurposing in other diseases include the use of paromomycin (from antibiotic in acute and chronic intestinal amebiasis to visceral and cutaneous leishmaniasis) (Ben Salah *et al.*, 2013), doxycycline (from bacteriostatic to antimalarial) (Tan *et al.*, 2011), miltefosine (from cancer to leishmaniasis) (Dorlo *et al.*, 2012), allopurinol (from cancer to gout) (Yasuda *et al.*, 2008), amantadine (from antiviral to tremors) (Gironell *et al.*, 2006), atomoxetine (from antidepressant to attention deficit hyperactivity disorder) (Turgay, 2005), colchicine (from gout to post-pericardiotomy syndrome) (Imazio *et al.*, 2010), and bromocriptine (from Parkinson's disease to type 2 diabetes) (Shaughnessy, 2011). Some examples of repurposed drugs used for the previous counterpart of SARS-CoV-2, *i.e.*, SARS and Middle East Respiratory Syndrome (MERS), include nitazoxanide (Rossignol, 2016), hydroxychloroquine (Zhou *et al.*, 2020a), emetine (Sharif-Yakan *et al.*, 2014), terconazole (Omrani *et al.*, 2015), lopinavir (Chan *et al.*, 2015), ritonavir (Chan *et al.*, 2015), ribavirin (Khalili *et al.*, 2020), homoharringtonine (Mustafa *et al.*, 2018), *etc.* The drugs for repurposing for the treatment of COVID-19 disease fall into multiple categories possessing various essential mechanisms. The essential categories include antivirals, anticancer, Angiotensin Converting Enzyme-Renin–Angiotensin–Aldosterone system (ACE-RAAS) inhibitors, anti-inflammatory, immune modulators, antibiotics, antirheumatics, *etc.* Besides this, some of the herbal drugs and nutraceuticals have also exhibited significant inhibitory potential against SARS-CoV-2 (Khan *et al.*, 2020, Liu *et al.*, 2020b).

SUBJECT INDEX

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Varun Garg

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