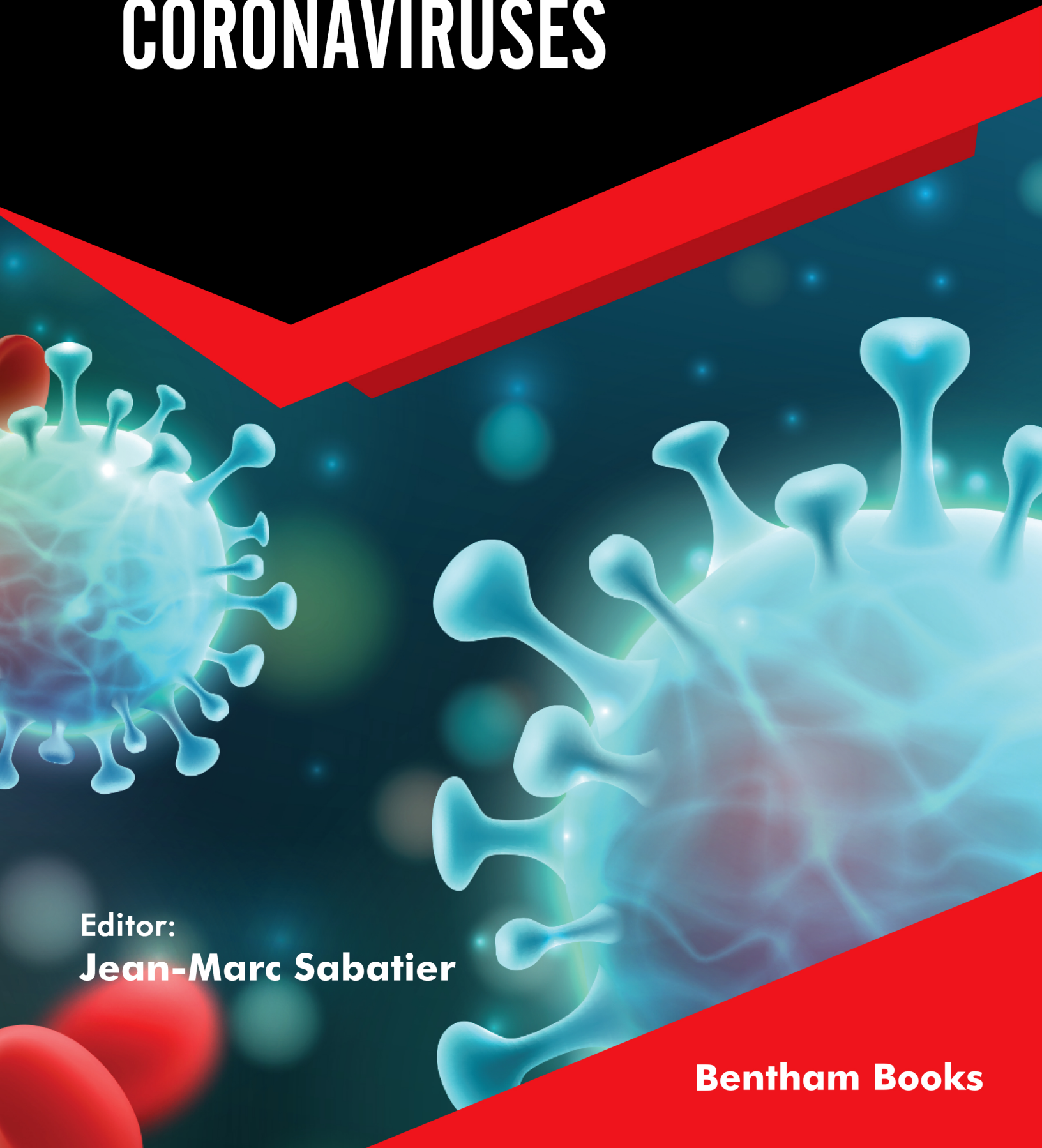
CORONAVIRUSES



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PREFACE

In this still pandemic period of SARS-CoV-2 (and its variants, especially 'Delta' variant) infection that is responsible for Covid-19, the scientific literature on these viruses and related cellular targets is crucial to help the researchers/virologists and clinicians from all countries to develop a new generation of safer and more effective vaccines, as well as treatments to cure the more or less severe diseases and damages to the many organs and tissues of SARS-CoV-2-infected people. This second book on coronaviruses mainly brings together some useful information regarding the prevention/vaccination, and chemotherapies to the potential treatment of coronavirus infections. The collection combines eight chapters titled: (1) Broad-spectrum antivirals to combat covid-19: The reality and challenges (chapter 1), (2) Covid-19: Preventive and protective control management strategies (chapter 2), (3) Plant-derived extracts and bioactive compounds against coronavirus progression: preventive effects, mechanistic aspects, and structures (chapter 3), (4) Gastroenteritis: symptoms and epidemiology of SARS-CoV-2 (chapter 4), (5) The chronicles of coronavirus: A Chinese king who conquered the entire world (chapter 5), (6) Traditional medicine as a natural remedy in ARDS & Covid-19 (chapter 6), (7) Molecular pathogenesis of human coronaviruses of 21st century (chapter 7), (8) COVID-19, mental health and neuropathophysiology of pain related to temporomandibular disorder (chapter 8).

Such a novel book compiling key data on SARS-CoV-2 and Covid-19 actually represents a tool of the utmost value for all researchers working on these research fields. It should also be of great interest to clinicians who are facing an overgrowing number of individuals with Covid-19. The data from 20th October 2021 give ca. 242 million cases of SARS-CoV-2 infection worldwide, with over 4.9 million deaths.

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CHAPTER 1

Broad-Spectrum Antivirals to Combat COVID-19: the Reality and Challenges

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Abstract: Viral infections, which lack effective treatment, have posed an ongoing threat to human health. Most approved antiviral agents selectively target a single virus, providing a "one drug-one bug" solution. However, this approach has limited efficacy, particularly with emerging and re-emerging viruses with no specific, licensed antiviral drug or vaccine.

Since the outbreak of the COVID-19 pandemic, tremendous studies have focused on the effect of some (broad-spectrum) antiviral agents on this emerging virus. The concept of broad-spectrum antivirals refers to the group of drugs with the capability of combating more than one virus rather than "one drug-one bug" agents. This approach may offer a new horizon for the management of emerging viral threats.

Among BSAs, nucleotide and nucleoside analogs target enzymatic functions shared by some viruses, thus, inhibit their replication. An alternative approach of BSA agents is to target host factors commonly required by multiple viral pathogens, on which the viruses intimately rely. For example, anti-malarial agents (chloroquine and hydroxychloroquine) inhibit acidification of endosomes, an essential process for uncoating of some RNA viruses, kinase inhibitors impair intracellular viral trafficking, and statins attenuate replication of some enveloped viruses.

In this review, we will shed light on BSA agents with potential efficacy against SARS-CoV-2 infection. The time-consuming process of new drug development makes repositioning drugs, already approved for use in humans, the only solution to the epidemic of sudden infectious diseases as COVID-19.

Keywords: Antiviral, Arbidol, Baricitinib, Camostat, COVID-19, Favipiravir, Imatinib, Niclosamide, Nitazoxanide, Remdesivir, Ribavirin, Sofosbuvir.

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Jean-Marc Sabatier (Ed.)

INTRODUCTION

In the past two decades, humanity has been exposed to several successive epidemics including the emergence of the severe acute respiratory syndrome (SARS-CoV-1) in 2003, Middle East respiratory syndrome (MERS) in 2013, Ebola virus disease in 2014, and currently, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) outbreak that represents an unprecedented public health challenge imposing great impact on nearly all countries around the world. The constant threat with the emergence of new strains of viruses has necessitated the search for novel effective therapeutic options.

Despite high species diversity, viruses share key elements that are essential for the design of therapeutic targets [1]. Although targeting specific viral factors *via* a "one drug, one bug" approach demonstrated measurable success in treating some viral infections such as influenza virus and hepatitis C virus, this approach is expensive, time-consuming, and more importantly, is associated with the rapid emergence of drug resistance [2]. Consequently, the concept of broad-spectrum antiviral drugs has been emphasized rather than developing drugs that are targeted to every specific virus. In this context, targeting common enzymes or proteins crucial in the life cycle of viruses or targeting host factors exploited by multiple viruses could provide broad-spectrum coverage for treating emerging viral infections [3, 4].

SARS-CoV-2, a member of the coronavirus family, has a very similar genome sequence identity with the SARS virus, and to a lesser extent with the MERS virus [5]. Moreover, the pathological features of those devastating virus infections are substantially similar. Hence, drugs that have been used previously to treat SARS or MERS may have the potential in treating patients with SARS-CoV-2 [6]. Coronaviruses (CoVs) undergo a distinct replication cycle, involving virion entry, RNA genome replication and transcription of viral mRNAs, protein translation, virion assembly, and packaging in the host cell, after which viral particles are released [7].

Coronaviruses specify two groups of (druggable) proteins; structural proteins and non-structural proteins. The structural proteins are functionally conserved among very closely related viruses. They include Spike (S), Membrane (M), Envelope (E), and Nucleocapsid (N) [8]. These proteins perform important functions in the viral life cycle: S is the main determinant of cell tropism, host range, and viral entry; E facilitates viral assembly and release, and has viroporin activity; M maintains the membrane structure of the virion, and N encapsidates the viral RNA genome [9]. Non-structural proteins are more conserved among CoVs and they are involved in essential functions of the viral lifecycle, such as 3C-like protease

(3CLpro; nsp3), papain-like Protease (PLpro; nsp5), and RNA-dependent RNA polymerase (RdRp; nsp12) [10]. These proteins are critical to the viral life cycle and provide potential targets for drug therapies.

On the other hand, several host factors have been identified to regulate signaling proteins crucial for the replication of viruses. Targeting host cell factors provides a different strategy against viral infections especially for those for which no effective treatment exists yet. An advantage of this strategy is that host factors do not undergo the same mutation rate that is seen for genomes of viruses. Furthermore, it may provide additive and possibly synergistic effects in combination with other strategies being developed to combat emerging viral infections.

Here, we will review the antiviral drug with broad-spectrum activity and its relevance in the treatment of coronavirus as per available data of clinical studies.

DRUGS TARGETING ENTRY PROCESS

Coronaviruses go through a staged entry process involving virion binding, receptor-mediated endocytosis, intracellular trafficking of virions to endosomes, and protease-dependent cleavage of spike (S) protein to facilitate fusion of the virion membrane to the endosomal membrane and deposition of the nucleocapsid into the cytoplasm [11, 12].

The membrane fusion relies on the expression of fusogenic glycoproteins on infected cell surfaces. Both viral envelope proteins and host cellular proteins are crucial for this process, hence providing potential antiviral therapeutic targets.

Viral Envelope Proteins

The spike (S) glycoprotein, a key immunogenic CoV antigen, is essential for virus-host cell receptor interactions. It exists in trimeric forms, giving them their characteristic corona structures [13]. The S protein is embedded in viral envelopes and mediates a crucial role in the entry of viral particles into the host cell [14]. It includes two functionally distinct subunits; S1 and S2 subunits, which process by cellular proteases to remain activated. The S1 subunit of SARS and also SARS-CoV-2 contains a receptor-binding domain (RBD) that binds to angiotensin-converting enzyme 2 (ACE2) receptors to mediate viral entry [15, 7]. The S2 domain is responsible for the fusion of the viral envelope with the cell membrane through its putative fusion peptide region. It has been reported that the RBD domain of SARS CoV-2 Spike (S-new; Sn) has a higher binding affinity for the ACE2 receptor than that of SARS Spike (S-old; So), while the S2 proteins of

CHAPTER 2

COVID19: Preventive and Protective Control Management Strategies

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Abstract: COVID-19 was identified as a global pandemic by the World Health Organization on March 11, 2020. The uncontrolled transmission of COVID-19 (Coronavirus Disease-2019) in almost 215 countries has posed a serious health issue among the world population. Cases of COVID-19 have emerged from the Huanan seafood market in Wuhan, South China, in December 2019 and have been rapidly spreading throughout the world since then. In this chapter, we have tried to extract data from various research reports, WHO guidelines, and other published articles to summarize the prevention strategies for COVID-19. This disease causes varying degrees of illness in patients like fever, cough, sore throat, breathlessness, fatigue, and other related symptoms. There are no drugs or other therapeutics presently approved by the U.S. Food and Drug Administration (FDA) to prevent or treat COVID-19. Current clinical management includes infection prevention, control measures, and supportive care through anti-viral, anti-microbial as well as immuno-modulating drugs as first-line treatment, followed by symptomatic treatment and oxygen therapy. Besides drugs, plasma convalescent therapy is being utilized in serious patients, but most of the vaccine candidates developed against SARS-CoV-2 are in the clinical trial stages. It is necessary to identify the potential cases as early as possible and isolate the vulnerable population from the confirmed cases of COVID-19, to prevent the potential transmission of infection to healthy people, other patients, and health care staff. Early protection, early identification, early diagnosis, and early isolation are crucial to combat the COVID-19 outbreak. Improved personal protection and hygiene management at community levels should be officially endorsed to protect the population from infections. Proper arrangement of medical resources (*i.e.*, oxygen supply, ventilators, PPE kits, gloves, sanitizer) can prevent the crucial damage caused by the disease. Another pressing need of the hour is to promptly discriminate patients with COVID-19 from other febrile diseases. Thus, the need of the hour is to develop rapid and accurate diagnostic technologies that can help the world to win the war against such viral pandemics.

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Jean-Marc Sabatier (Ed.)

Keywords: Breathlessness, COVID-19, Oxygen supply, Preventive strategies, SARS-CoV-2, Ventilators.

INTRODUCTION

Over a long period of time, viral diseases have emerged as one of the serious and a major threat to public health and are still continuing to affect the world population as per the report of the World Health Organization (WHO). In the last twenty years, diverse viral epidemics like SARS-CoV (2002 to 2003), H1N1 influenza (2009), and MERS-CoV(2012) have been reported. Towards the beginning of December 2019, there was a sudden occurrence and outbreak of a new type of viral cases in Wuhan, Hubei Province of China. This newly encountered biological organism was named as 2019 novel coronavirus by the World Health Organization that was later on renamed as SARS-CoV-2. The word "Corona" refers to a crown shape-like structure as the surface of the virus exhibits crown-like projections. Coronavirus is a club-shaped RNA virus that is single-stranded with a size ranging from 80-100 nm. The Hunan seafood market at Wuhan, China, was assumed to be the main source of novel coronavirus [1].

The commonly associated signs and symptoms include fever, cough, cold, difficulty in breathing and problems associated with the respiratory system. Also, the conditions like total damage of the kidneys, respiratory syndromes, and death of the patients may result depending upon the severity of the disease (Fig. **1**). There are seven categories of CoV that have the capability of infecting human beings. Out of the seven types, HCoV-NL63 and HCoV-229E are the two α-CoVs. SARS-CoV, HCoV-HKU1, HCoV-OC43, and MERS-CoV are the four types of β-CoVs, and the last type is recognized as SARS-CoV2. The data of genomic study analysis indicated that the genetic sequence exhibited by SARS-CoV2 has 96% similarity to that of bats SARS-CoV (SARSr-CoV-RaTG13), and hence it was thought that SARS-CoV has originated from bats. It was since 9th January 2020 that the disease caused by the novel coronavirus was termed COVID-19 after the submission of the complete genetic sequence of SARS-CoV2 by Chinese researchers. With time as the viruses have become resistant to all the treatment strategies, hence it has potentially evolved as a pandemic affecting a huge population worldwide and thereby threatening public health. Outside China, the number of COVID-19 cases has increased to 13 times, and the countries affected by COVID-19 have increased by three times (Table **1**). Further, more than 1,18,000 cases and 4,000 deaths have been reported in 114 countries, and thereby, WHO declared the COVID-19 a pandemic on 11th March, 2020 [1, 2].

Table 1. List of total confirmed cases and death of COVID-19 globally in 2020 [2].

Country	Total Confirmed Cases	Total Deaths
United States of America	3,544,143	137,674
Brazil	2,046,328	77,851
India	1,077,618	26,816
Russian Federation	771,546	12,342
South Africa	350,879	4,948
Peru	345,537	12,799
Mexico	331,298	38,310
Chile	328,846	8,445
The United Kingdom	294,070	45,273
Iran	271,606	13,979

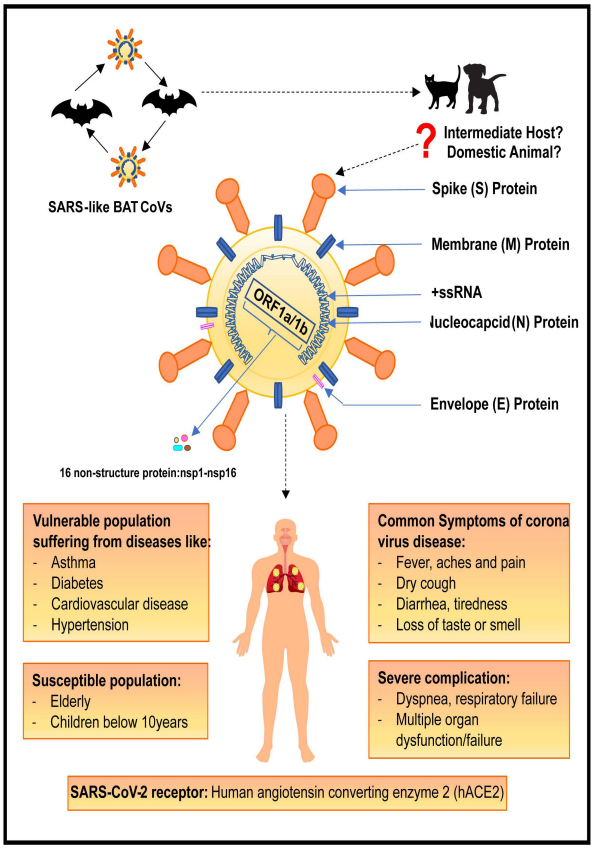

Fig. (1). Transmission of Coronaviruses to the human body (Self-created by authors).

CHAPTER 3

Plant-derived Extracts and Bioactive Compounds against Coronavirus Progression: Preventive Effects, Mechanistic Aspects, and Structures

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Abstract: Coronaviruses (CoVs) are associated with several infectious outbreaks in humans, beginning with severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012. Recently, the World Health Organization (WHO) announced the global outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in December 2019. There are currently no natural or synthetic drugs that inhibit SARS-CoV2. Because of the COVID-19 outbreak, many people have returned to the use of complementary or traditional medicinal therapies for prophylaxis or treatment. Herbal extracts and their purified natural compounds provide a platform for the development of novel antiviral candidates. Effective drugs may be designed based on the chemical structure of natural compounds that exhibit potential effects. Researchers have primarily focused on 3-chymotrypsin-like protease (3CLpro), papain-like protease (PL^{pro}), RNA-dependent RNA polymerase, and spike (S) proteins as drug targets for SARS-CoV. Furthermore, phylogenetic studies of the viral genome have provided evidence of a close similarity between SARS-CoV2 and SARS-CoV1. Here, we review the literature with respect to plant extracts from different families that have been examined for antiviral activity against coronavirus diseases and explore the underlying mechanisms. We also discuss the structures of promising natural compounds representing different categories that serve as SARS-CoV chemical inhibitors. Hopefully, this chapter will provide a valuable tool for scientists interested in developing effective naturally derived anti-SARS-CoV-2 drugs for the management of COVID-19 development and progression.

Keywords: Antiviral, Coronavirus, Outbreak, Protease, Respiratory, Traditional medicine.

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INTRODUCTION

Several infectious outbreaks have been associated with coronaviruses in humans, beginning with SARS in 2003 and Middle East respiratory syndrome (MERS) in 2012 [1, 2]. On January 30, 2020, an outbreak of viral pneumonia was caused by a novel coronavirus (SARS-CoV-2) in Wuhan, China [3]. On March 11, the WHO announced an epidemic outbreak of coronavirus disease 2019 (COVID-19) [4]. By April 12, 2020, 1,696,588 confirmed cases of infection were reported with 105,952 deaths [5]. The rapid transmission of COVID-19 resulted in a major global risk with confirmed cases occurring in 213 countries and a global fatality rate of approximately 3.92% [6].

Coronaviruses are enveloped viruses with a positive-sense, single-stranded RNA genome and a helical symmetry [7]. They belong to the family Coronaviridae and are divided into three groups based on serological cross-reactivity and nucleotide sequence [7]. Group I coronaviruses include animal pathogens, such as porcine transmissible gastroenteritis coronavirus (TGEV) and human coronavirus (HCoV-229E) [7]. Group II includes pathogens of veterinary relevance, such as murine coronavirus and mouse hepatitis virus (MHV)-JHM strain and human severe acute respiratory syndrome coronavirus (SARS-CoV). Group III includes avian coronaviruses [8]. The symptoms of coronavirus infection primarily occur in the upper respiratory and gastrointestinal tracts of animals and mammals [9]. Recently, the phylogenetic studies of the viral genome provide evidence of a close similarity (approximately 89.1%) between SARS-CoV-2 and SARS-CoV-1 [3].

Cumulative experience for the rational use of herbal medicine, trial and error, and the progression of the chemistry and biology fields has resulted in the development of herbal drugs and their extracts. This has led to a breakthrough in the treatment of many serious diseases, and these developments, in contrast to ancient ones, are primarily the result of modern western civilization. Since the 18th century, major developments in chemistry have occurred, and scientists were prompted to isolate active ingredients from herbal extracts. For example, the isolation of the antimalarial drug quinine from the Cinchona extract [10], the cardiotonic and antiarrthymeic drug digoxin from the digitalis extract [11], the potent analgesic morphine from papaver [12] and the anticancer drug paclitaxel from *Taxsus brevefolia* [13] took place. Moreover, these isolated molecules have inspired scientists to develop “similar” drugs based on natural “templates”. Thus, aspirin was synthesized to simulate the action of salicylic acid isolated from the Willow bark [14]; the discovery of natural and semi-synthetic antibiotics was based on the isolation of penicillin from the fungus *Penicillium notatum* [15] and the synthesis of the antimalarial drug chloroquine was based on the structure of quinine [16].

Currently, scientists are actively searching for effective antiviral agents that effectively combat COVID-19 [17]. Unfortunately, there are presently no specific antiviral drugs for the control of COVID-19. As a result, the development of safe, effective, and highly potent anti-coronaviral agents for controlling the potential emergence of pandemic coronaviruses is an urgent need [7]. Medicinal plants, especially those used in traditional medicine, have attracted significant attention because they contain bioactive compounds that may be developed to treat various diseases with minimal side effects [18]. Notably, approximately 10% of more than 4,000 plant species have demonstrated significant *in vitro* antiviral potential [19].

With respect to COVID-19, we dedicated this chapter to providing an update on the effectiveness of natural products that exhibit antiviral activity against different strains of coronavirus. The chapter is divided into two sections: medicinal plants including plant extracts and essential oils, and natural compounds. Hopefully, this review will assist scientists in the development of new candidate drugs to combat the unlimited spread of COVID-19.

MATERIALS AND METHODS

The data were collected through an electronic search using PubMed, SciFinder, Scirus, Google Scholar, and Web of Science, as well as conducting a library search for articles published in peer-reviewed journals.

RESULTS AND DISCUSSION

Medicinal Plants with Antiviral Activity against Coronavirus

Plant Extracts

A screening study was employed to evaluate the potential of *Cimicifuga rhizoma*, *Meliae cortex*, *Coptidis rhizoma*, *Phellodendron cortex,* and *Sophora subprostrata* extracts against various strains of coronavirus [20]. The extracts effectively decreased mouse hepatitis virus A59 (MHV-A59) production and intracellular viral RNA and protein expression with EC_{50} values ranging from 2.00 to 27.50 μg/ml. These extracts also significantly decreased porcine epidemic diarrhea virus (PEDV) production and, to a less extent, decreased vesicular stomatitis virus production *in vitro*. Another study conducted by the same group demonstrated that *Sophora flavescens* radix, *Sanguisorba officinalis* L. radix, *Acanthopanax gracilistylus* W.W. Smith cortex, and *Torilis arvensis* fructus were effective against MHV-A59 replication in infected cells [21]. Mechanistically, the inhibitory effect was attributed to the induction of cyclooxygenase-2 (COX-2) expression through extracellular signal-related kinase and p38 activation.

CHAPTER 4

Gastroenteritis: Symptoms and Epidemiology of SARS-CoV-2

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Abstract: Previous studies on the coronavirus (CoVID-19) have shown that respiratory symptoms such as fever, dry cough, and shortness of breath are mainly the common manifestations at the onset of the infection. These symptoms are largely similar to severe acute respiratory syndrome (SARS), which prevailed in 2003, and the Middle East respiratory syndrome (MERS) in 2012, indicating droplet and contact transmission to be the reason for transmission. However, it is widely accepted that a range of common attributes, like diarrhea, nausea, vomiting, and abdominal discomfort, can be observed among various affected populations, along with an early and mild onset commonly followed by typical respiratory symptoms. Increasing affirmation from several recent research works on SARS-CoV-2 has indicated that the gastrointestinal tract (intestine) epithelium is a favorable host to SARS-CoV-2 coronavirus particles. These findings are confirmed by the viral detection in biopsy specimens and stool samples of even the positive patients, thus explaining at least partially the gastrointestinal symptoms in the patients. Additionally, the wastewater-based epidemiology studies being done by various countries suggest that individuals can start shedding the virus particles in the feces long before any of the key symptoms could be manifested or before the patients could be clinically diagnosed. These findings have ignited the questions on potential recurrence and transmission of COVID-19 from persistent fecal shedding from the infected individuals.

Keywords: COVID-19, Faecal-oral Transmission, Gastroenteritis, WBE.

INTRODUCTION

Coronaviruses are small in size (65 –125 nm in diameter) and contain single-stranded RNA as nucleic material, ranging from 26 to 32 kbs in length. The coronaviruses family have subgroups including alpha (a), beta (b), gamma (c), and delta (d) coronavirus. All four genera of coronaviruses can be found in birds and mammals, including bats. The first coronavirus was avian infectious bronchitis viruses (IBV) which caused disease in chickens and humans [1, 2].

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Various other important coronaviruses such as SARS- CoV, MERS-CoV, and SARS-CoV-2 were found to be correlated with inflammations in humans [3, 4]. Previously it was thought that these viruses cause infection in animals until a severe acute respiratory syndrome (SARS) outbreak occurred in Guangdong, China, in 2002 [5], and Middle East respiratory syndrome coronavirus (MERS-CoV) in Middle Eastern countries [6]. The separate cases of pneumonia of unrevealed origin in late December 2019, from China, were reported to be caused by a novel coronavirus which was later designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2) and defined as Coronavirus Disease 2019 (COVID-19).

Firstly, on 29th December, 4 cases were reported from Seafood wholesale market in Wuhan, a central city in China [7]. After investigation, the local Center for Disease Control (CDC) confirmed additional patients connected with a similar market and reported on 30 December 2019 to China CDC [7]. World Health Organization (WHO) was enlightened about the cases of pneumonia of unknown etiology on the next day by China CDC [8], and a level 2 emergency response was launched by China CDC on 6 January 2020 [9]. Until 7 January 2020, the causative factor was not recognized; Chinese authorities isolated a new type of coronavirus [8], and on 10 January 2020, the sequence of the SARS-CoV-2 genome was first shared by China [10]. The development of molecular diagnostic methods for the isolation and identification of SARS-CoV-2 facilitated the confirmation of the infected patients. As of 21 January, 270 cases were confirmed from Wuhan [8].

Wuhan, a central city in China, underwent lockdown on 23 January 2020, warning people worldwide about an emerging novel coronavirus, which poses a major threat to public health [8]. The entire china was taken by the storm of 2019 novel Coronavirus, which crossed the borders of China to reach across the globe immediately, hitting the worldwide score of 2,544,792 confirmed cases and 175,694 deaths, reported as per World Health Organization (WHO) Situation Report– 94 of 23rd of April 2020 [11].

SARS-COV-2 - THE PATHOGEN CHARACTERISTICS

SARS-CoV-2 –virion looks like a spherical shape when observed by transmission electron microscopy imaging, with pleomorphism [12]. SARS- CoV-2 morphology was consistent with the Coronaviridae family with a genome enveloped in protein, with 38% G+C content consisting of six major open reading frames (ORFs) encoding non-structure proteins and structural proteins including spike glycoprotein, small envelope protein, matrix protein, and nucleocapsid protein and other accessory genes [13]. The genome sequences of coronavirus

isolated from different patients showed conservation, suggesting that the virus evolves recently [14]. S glycoprotein of SARS- CoV-2 helps in binding host cell receptors, angiotensin-converting enzyme 2 (ACE2), which is a critical step for virus entry. Etiologies evolve with the interactions of host proteins with the proteins of the virus, leading to infection susceptibility and progression.

EPIDEMIOLOGY AND TRANSMISSION

The dissemination of SARS-CoV-2 from human to human occurs in people who are personally in contact with patients or incubation carriers, mainly between family members, relatives, and friends [15]. In contrast, the transmission in health care workers in hospital-acquired infection in the case of SARS-CoV is 33–42% and 62–79% in the case of MERS [16]. But the main route of SARS-CoV-2 transmission was found to be immediate exposure with host animals or wild animals.

However, the origin and dissemination routine of SARS-CoV-2 remain difficult to track down. The respiratory tract is the major source of COVID-19 spreading by droplets, respiratory secretions, and direct contact. Also, the transmission of the virus was found to be multiple as SARS-CoV-2 was isolated from fecal swabs and blood. The patients with COVID-19 infection showed specific similar symptoms, such as fever (88.7%), malaise, cough (67.8%), sputum production (33.4%), sore throat (13.9%), headache (13.6%), and shortness of breath (18.6%) with 1-14 days of incubation but few patients presented Acute respiratory distress syndrome (ARDS), respiratory failure, multiple organ failure, and even death [17, 18]. Gastrointestinal symptoms such as diarrhea (3.8%) and vomiting (5.0%) were exhibited in few numbers of patients. The dominant symptoms were fever and cough, whereas gastrointestinal symptoms and upper respiratory symptoms were rare.

As the severity of illness in critically ill patients increases, the fatality rate also increases and can reach up to 49%. Unfortunately, no definite curative alternatives are accessible; only protective means can be put in an application instantly [19]. COVID-19 has an elevated figure of asymptomatic COVID- 19 carriers, due to which there is a higher level of transmissibility compared to SARS and MERS [20].

In China, a study published by the Chinese Centre for Disease Control and Prevention (CCDC) reported a case fatality rate of 2.3% for SARS CoV-2 [21] which is significantly lower than that of SARS (9.5%) and MERS (34.4%) [9].

Transmission of the virus from human to human is mainly through respiratory tract droplets expelled out from an infected person’s cough or sneeze and are

CHAPTER 5

The Chronicles of Coronavirus: A Chinese King Who Conquered the Entire World

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Abstract: Coronaviruses cause infections in birds and rodents, but these viruses have been able to infect the human in the last few decades. The Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 and the Middle East Respiratory Syndrome (MERS) in 2008 revealed the lethality of coronaviruses, as these viruses cross the species barrier and infect humans. An epidemic of novel Coronavirus that emerged in province Hubei, of which Wuhan was the epicenter, linked the number of cases with pneumonia-like symptoms to the seafood market in Wuhan, China. The human epithelial cells were used for the isolation of novel coronavirus that was diagnosed through the use of unbiased sequencing, later named nCoV-2019. Based on the information, there was evidence of transmission in humans that occurred because of close contact from the middle of December 2019. In recent times, the infection has been identified in other countries around the world, infecting millions of people. This review aims to assess the latest information regarding COVID-19 and compares it with previous knowledge reported regarding it. Most progress has been made on COVID-19, highlighting the specific structural requirements for its functions in the nCOV-19 life cycle and the mechanism behind its pathogenesis.

Keywords: COVID-19, Diagnostics, MERS, NCoV-19, NS Proteins, Pathogenesis, SARS, SARS-CoV-2, The Structure of SARS-CoV-2, Transmission.

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Jean-Marc Sabatier (Ed.)

INTRODUCTION

Coronaviruses include RNA viruses of veterinary and medical concern. All coronaviruses are characterized by spherically enveloped particles with prominent surface projections, resembling the Corona of Sun (Fig. **1**). Coronaviruses belong to order Nidovirales of the family Coronaviridae, subfamily Coronavirinae. These viruses are single-stranded positive-sense RNA viruses with genome size varying from 26 to 32 kilobases that make them the viruses with the largest genome among RNA viruses [1]. Based on the antigenic and genetic criteria, Coronaviruses have been organized into four groups: Alpha Coronavirus includes; FECV (Feline Enteric Coronavirus), PRCoV (Porcine Respiratory Coronavirus), Feline (FCoV), Porcine TGEV (Transmissible Gastro- Enteritis Virus), FIPV (Feline Infectious Peritonitis Virus), Porcine PEDV (Epidemic Diarrhea Virus), Canine CCoV, HCoV-229E, HCoVNL63 and Bat Coronaviruses, Beta Coronavirus include; HCoV-HKU1, MERS-CoV, HCoV-OC43, SARS-CoV, Murine coronavirus (MHV) and Bovine Coronavirus (BCoV), Gamma Coronaviruses like Infectious bronchitis virus (IBV) are specific to birds except for Beluga whale Coronavirus while Delta Coronaviruses were created in 2012 by the regrouping of various human Coronaviruses HKU11, HKU12, HKU13 and animal viruses (Fig. **2**) [2, 3].

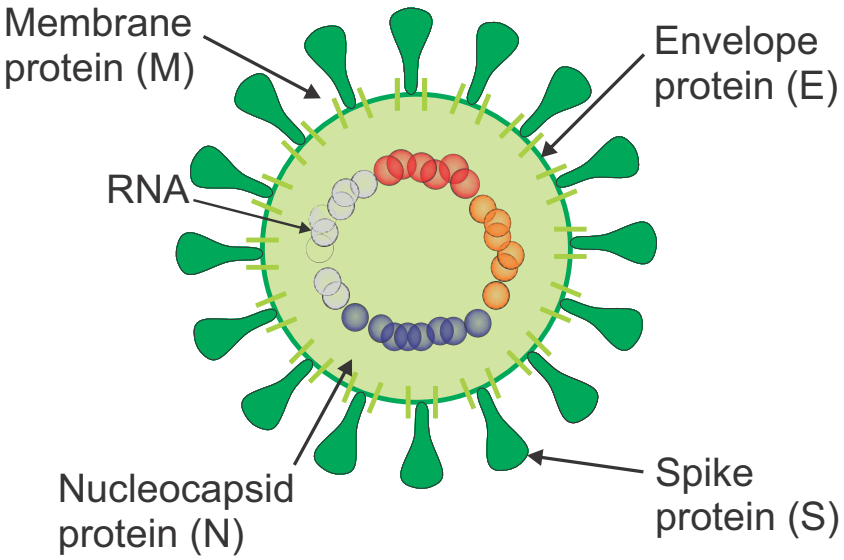

Fig. (1). Structural proteins of Coronavirus.

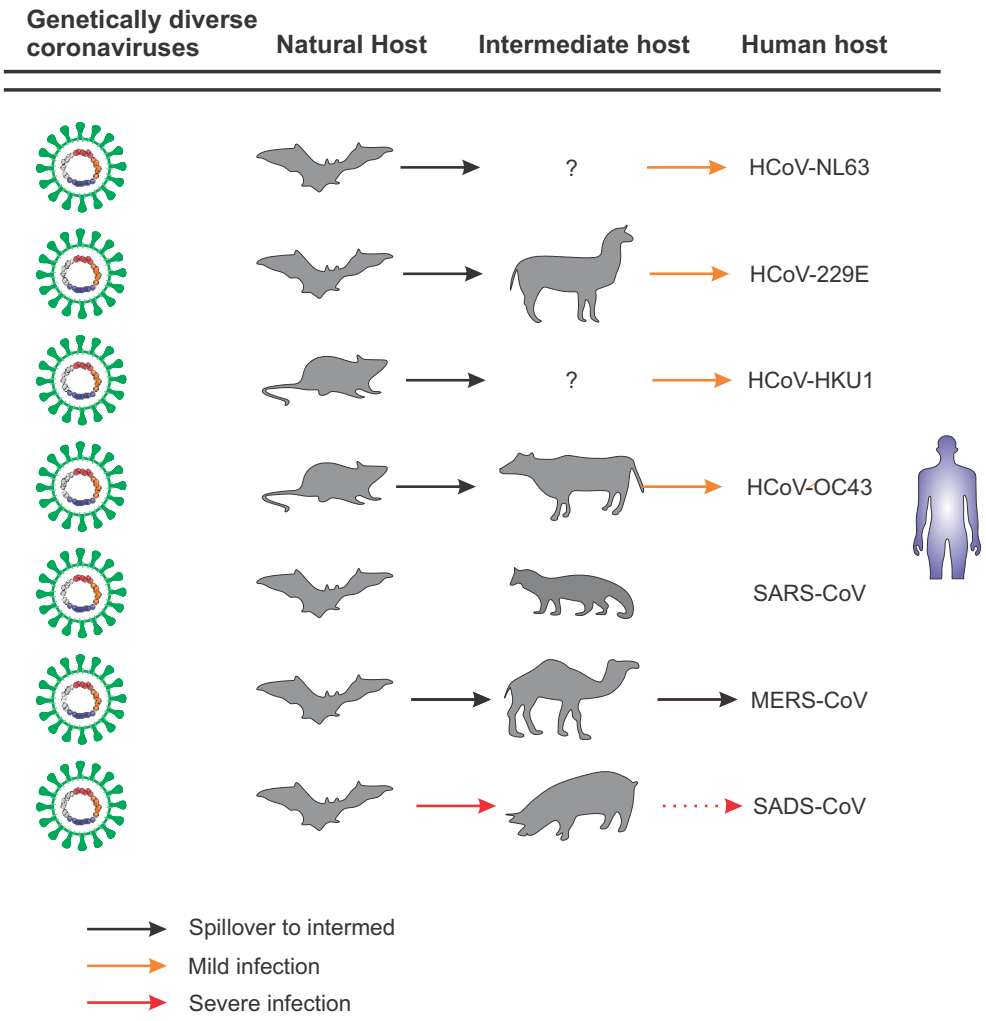

Fig. (2). Animal origins of human Coronaviruses.

Primarily, coronaviruses were thought to be enzootic infections causing disease in animals and birds only, but some viruses have crossed the species barrier of humans and animals, proceeding to establish zoonotic diseases in humans. These viruses may lead to upper respiratory tract infections that mimic a common cold, such as lower respiratory tract infections such as influenza, bronchitis and extreme acute air syndromes. These symptoms are similar in all types of coronaviruses the viruses affecting the respiratory tract [1]. The symptoms specific to COVID-19 are fever, dyspnea, cough, fatigue and less frequent gastrointestinal and anosmia [4].

CHAPTER 6

Traditional Medicine as Natural Remedy in ARDS & COVID-19 Through Interleukins

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Abstract: SARS-Corona-Virus-2 related disease (COVID-19) is a 2019 outbreak and was declared as a pandemic by WHO in March 2020. The high mortality rate in humans with SARS-CoV-2 has been attributed to its effects on major organs and primarily on the lungs. Therefore, it is extremely imperative to identify effective strategies for the prevention and treatment that can cease or reverse the inflammatory process associated with acute lung injury, ARDS, and multi-organ failure in COVID-19 patients. Inflammation to lungs through cytokine storm [also known as cytokine release syndrome (CRS)] is mediated through many cytokines, and IL-17 is one amongst them. We have experimentally demonstrated IL-17 responses in autoimmune/inflammatory disorders through *Boerhavia erecta* L *in vitro* and *in vivo* models recently, and further, propose this herbal medicine in this review chapter as a potential treatment option for mild to moderate acute respiratory distress syndrome (ARDS) in COVID-19 patients.

Keywords: ARDS, Autoimmune, *Boerhavia erecta* L, COVID-19, CRS, Cytokine, Inflammation, Interleukins, Mortality, Prevention, Traditional.

INTRODUCTION TO COVID-19

Severe acute respiratory syndrome coronavirus 2 is the strain of coronavirus that is responsible for coronavirus disease 2019 (COVID-19) [1]. This is also referred to as 2019 novel coronavirus (2019-nCoV) or human coronavirus 2019 (HCoV-19), the pulmonary infection a principle reason for the COVID-19 disease. Approximately 1/3rd of infected patients develop mild pulmonary inflammation in severity, resulting in acute lung injury that finally leads to acute respiratory distress syndrome (ARDS) over 14 days [2]. As of 22 November 2020, the global disease burden (Johns Hopkins University - https://coronavirus.jhu.edu/map.html) estimate is over 58.64 million infections and almost 1,388,068 deaths worldwide.

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The primary direct reason for the transmission was presumed to occur initially *via* coughs and sneezes within a range of about 6 ft. and few recent studies confirmed that COVID-19 may be airborne. Whereas, indirect transmission through contaminated surfaces could be another plausible cause of this debilitating disease. One has to take all precautions to avoid the group transmission of an infectious disease.

SARS-CoV-2 causes greater risk in geriatric patients having evidence of co-morbid conditions such as heart, liver and, kidney diseases and often die of their original comorbidities and this has triggered a need for alternative treatments that can stop any untoward outcomes [3]. Therefore, while treating pneumonia, importance has to be given for the treatment of any underlying diseases of the individual. SARS-CoV-2 causes damage to the lungs and other major organs, including blood and the immune system [4]. Eventually, patients succumb to multiple organ failure, shock, ARDS, heart, and renal failures [5]. The major reasons for such infection could be due to be pneumonia, characterized by bilateral infiltrates in addition to cough and fever. However, it has become extremely difficult for clinicians to differentiate it from other viral respiratory illnesses due to a lack of common clinical features [6]. Many patients had experienced symptoms of the disease in a lighter tone, but only a few patients experienced quick progression of their clinical symptoms over a week to 10 days. In the majority of the cases, lower zone consolidation of bilateral lobes of lungs was found maximum at 10-12 days from onset of symptoms. All such viral pneumonia symptoms like fever, fatigue, dry cough, and lymphopenia share common radiological features of COVID-19 [7]. Acute lung injury induced by both capillary leak of endothelial cells and cytokine storm was found to be the key elements in the immuno-pathology of ARDS and MODS (Multiple Organ Dysfunction Syndrome) associated with various forms of COVID-19 [8].

COVID-19 - GLOBAL CHALLENGES

COVID-19, since its outbreak during December 2019, has proved to be the most deleterious pandemic threat across the globe. Now it has emerged as a formidable task for the scientists to find a way out for the COVID-19. The major possible reason could be the COVID-19 virus's ability to replicate at a greater frequency. This results in new positive strands and multiplication of the viral progeny cells in the human cells. Recently, the biggest challenge for the researchers is that SARS-CoV-2 is found to have a high risk of mutation and therefore switches to a different form. This has caused a great challenge in developing the curative process (American Society for Microbiology, 2020). It has been established by a few researchers that SARS-CoV-2 has two types of strains, the 'L' and 'S' strains. Amongst these, the common L strain could have emerged from the S strain which

has a higher rate of infection in a short period and responsible for its fast replication rate inside the human host cell. By and large, this has become a huge challenge for the precise analysis and develop therapies in the short time available. It also exhibits a high rate of mutagenesis, and this made a difficult task for the scientists to analyze its genomic sequence and interaction with host cells [9]. Recent Global Financial Stability Report shows that the COVID pandemic has left a huge impact on the world's financial system, and if the crisis is not addressed immediately, it could affect global financial stability. Many large and small markets have seen declines of 30% or more since 2009. Many stress factors have also emerged in major funding markets, this includes both the global and Indian markets and seems to have repercussions for at least another 2 to 3 years.

PATHOLOGY OF ARDS (ACUTE RESPIRATORY DISTRESS SYNDROME) OR ALI (ACUTE LUNG INJURY)

ARDS is considered a severe form of acute lung injury (ALI). It generally surfaces when fluid fills up air sacs in the lungs which leads to a decrease in the amount of oxygen or elevated levels of carbon dioxide in the blood circulation. Thus ARDS deprives the major organs of sufficient oxygen supply eventually leading to organ failure. The most common symptoms of ARDS are muscle fatigue, difficulty in breathing (dyspnea, fever), discolored skin or nails, and CNS disorders. Such symptoms are largely caused by inhaling toxic chemicals or developing a severe infection such as pneumonia or overdosing on sedatives or tricyclic antidepressants, *etc*.

The Prima facie of ARDS treatment is to supply adequate amount of oxygen to prevent MODS by administering oxygen through invasive or non-invasive mechanical ventilators that supply air or oxygen *ad libitum* into the lungs. Secondly, fluid balance is another ARDS treatment method that involves adequate fluid intake and it helps in many cases. Large amounts of fluid in the body can cause fluid accumulation in the alveoli (air sac). However, on the other way around even extremely low quantities of fluids also can strain the major organs. Thus, patients with ARDS are prescribed medications to counter any adverse effects, which include analgesics to relieve pain, antibiotics for the infection, blood thinners to prevent disseminated intravascular coagulation (DIC). Further, the exudative (acute) phase that lasts 1 - 7 days involves inflammation through neutrophils that damage the alveolar epithelium, this increases its permeability and causes intra-alveolar hemorrhage and edema; this edema which is rich in proteins communicates with alveolar surfactants, thereby pulmonary compliance is minimized.

CHAPTER 7

Molecular Pathogenesis of Human Coronaviruses of 21st Century

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Abstract: Coronaviruses affect both humans and animals, causing respiratory, enteric, hepatic, and neurological diseases. Until the outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, coronaviruses were known to cause very mild infections in humans. However, the ongoing novel coronavirus disease (COVID-19) that emerged in December 2019 from Wuhan, Hubei province, China, is several folds critical than the disease caused by its predecessors, SARS and MERS coronaviruses of 2002 and 2012, respectively. The evidence shows that all the human coronaviruses of this century, including the ongoing pandemic SARS-CoV-2, were the result of zoonosis, crossing the animal species barrier, causing high morbidity and mortality in the human population. A large number of studies have provided an understanding of earlier SARS-CoV and MERS-CoV induced pathogenesis and host immune response. Immunopathogenesis of current SARS-CoV-2 has also been reported to a significant extent since its emergence. It is evident from the studies reported to date that all the above three human coronaviruses share similarities with respect to clinical symptoms caused, pathological conditions induced, and host immune response that leads to the disease progression to a larger extent. However, certain pathological features associated with SARS-CoV-2 infection are distinct and fatal from the features caused by the other two human coronaviruses. This chapter focuses on the studies related to immune response, molecular pathogenesis of all three human coronaviruses with an emphasis on SARS-CoV-2 and the immune evasion strategies stimulated by individual viral proteins and their driven mechanisms.

Keywords: ACE2, ARDS, COVID-19, Immune Evasion, Immune Response, MERS, Pathogenesis, Pneumonia, SARS-CoV, SARS-CoV-2.

INTRODUCTION

An outbreak of pneumonia ,a new public health crisis threatening the world,

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Jean-Marc Sabatier (Ed.)

emerged towards the end of December 2019 from Wuhan, Hubei province, China spreading across the globe. The pathogen-associated with pneumonia was identified as an unfamiliar coronavirus of zoonotic origin and was marked as 2019-nCoV by the World Health Organization (WHO). Since its sequence had shown genetic relatedness with SARS-CoV of 2002 and Bat SARS-like coronaviruses, it was renamed by the Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) as SARS-CoV-2 [1]. Later, on February 11, 2020, the disease was given the official name COVID-19. Globally, there have been more than 50 million confirmed cases of SARS-CoV-2 and more than 1.2 million deaths in 219 countries reported by the WHO, as of 9th November, 2020. In the 21st century, two human coronaviruses have caused outbreaks of pneumonia, severe acute respiratory syndrome (SARS) CoV of 2002 affecting 8096 persons with 774 deaths in 29 countries [2], and the middle east respiratory syndrome (MERS) CoV emerged in Arabian Peninsula in 2012 with more than 2510 cases with 866 deaths in 27 countries as per the report of WHO, Eastern Mediterranean Regional Office, Egypt. The ongoing SARS-CoV-2 associated mortality is lower than that of SARS and MERS, but the number of persons infected with SARS-CoV-2 is massive compared to the former two human coronaviral infections taken together. The transmission rate of SARS-CoV-2 is also much higher and has been spread to almost all the parts of the world, but the frequency of spread is reported to be different among the countries [3].

SARS-CoV-2 is so far the 7th member of the Coronaviridae family infecting humans. All the three human coronaviruses of this century are zoonotic in nature, triggering high morbidity and mortality in human populations [4 - 6]. SARS and MERS-CoVs originated from bats crossing the animal species barrier to infect humans through different intermediate hosts. The intermediate host for SARS-CoV is suspected to be the palm civets, whereas MERS-CoV was transmitted through the dromedary camels [7, 8]. However, the intermediate host for SARS-CoV-2 is still not known; whether this virus infected humans *via* direct transmission from a bat or through any transitional host is also not clear. Re-investigation of the published data, the genomic and evolutionary pieces of evidence have shown 91.02% sequence identity between Pangolin-CoV and SARS-CoV-2 and 90.55% with Bat-CoV RaTG13 [9], indicating the Pangolin origin of SARS-CoV-2. However, it needs to be substantiated with other pieces of evidence. Irrespective of its original source, the most probable hypothesis is that SARS-CoV-2 entered an insignificant number of humans, likely from an infected animal, and from there, the virus attained the ability to infect humans and spread through human-to-human transmission before the group of patients infected with SARS-CoV-2 was recognized [10]. Comprehensive sequence analysis and comparative study in conjunction with the relative synonymous codon usage

(RSCU) bias among different animal species based on the SARS-CoV-2 sequence suggest that the emergence of novel coronavirus could be the result of recombination between bat coronavirus and a coronavirus of unknown-origin [11]. The possible recombination that might have taken place within the viral spike glycoprotein resulted in the emergence of a highly pathogenic and virulent strain than the former two human coronaviruses. Coronaviruses are empowered with potent immune-evasion mechanisms that have the ability to target multiple aspects of innate immunity. SARS-CoV-2 initiates extensive production of cytokines, reduces the interferon responses, and suppresses the viral antigen presentation on both MHC class I and class II molecules [12].

Pathogenesis is the process through which a disease develops. Viral pathogenesis generally develops in two ways: cellular pathogenesis, *i.e*., direct damage caused to the cell by the virus, and immune pathogenesis, *i.e*., global damage caused due to increased host immune response to the infection. Most respiratory viruses trigger a critical immune pathogenic response with relatively minimal cellular damage. Pathogenesis begins with the entry of the virus into the host through its interaction with a cell surface receptor, followed by replication, production of progeny particles, and then dissemination to different target organs. Some infections are undetectable as the body's anti-viral immune defenses eliminate the virus before the onset of the disease. However, highly pathogenic viruses have self-engineered strategies to overcome these host defense mechanisms. The interaction of virulence factors with key host molecules determines the ability of the virus in the successful establishment of the infection and the disease severity [13]. The purpose of this chapter is to compare the molecular pathogenesis of the three human coronaviruses, SARS-CoV, MERS-CoV, and SARS-CoV-2, by discussing the following components: (1) the differences in their proteomes contributing to pathogenesis and comparison of the subtypes based on their virulence, (2) viral entry, tissue tropism, infection, transmission, (3) molecular pathogenesis, (4) immune response elicited and (5) immune evasion mechanisms and their involvement in the viral life cycle/disease process.

COMPARISON OF ALL THREE HUMAN CORONAVIRUSES

Proteome Comparison

The Coronaviridae family members are enveloped viruses with the largest positive-sense single-stranded RNA genome of about 25 - 30 kb. They have multiple open reading frames (ORFs) encoding for structural and non-structural proteins. The non-structural proteins, Nsp1 to 16 are produced from the proteolytic processing of ORF1a/ORF1ab polyprotein, which is the common mechanism in all three CoVs. Comparative analysis of SARS-CoV-2 proteome

CHAPTER 8

COVID-19, Mental Health and Neuropathophysiology of Pain Related to Temporomandibular Disorder

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Abstract: Temporomandibular disorders (TMDs) are a group of disorders related to pain and dysfunction that affect the temporomandibular joint (TMJ) and the masticatory system. TMD patients often suffer from orofacial pain and have symptoms that are less specific, including ear pain and ear fullness, tinnitus, dizziness, neck pain, and headache. Thus, individuals with TMD and orofacial pain deserve special attention, since neurological events such as headache, tinnitus, and muscle pain, which are present in these conditions, can also be found in cases of COVID-19. In addition, mental health disorders, such as anxiety and depression, are more common in patients with TMD than in the general population. Consequently, individuals with psychological disabilities, such as TMD patients, may have their pain perpetuated as a result. COVID-19 is not only affecting physical health — it has brought direct and indirect psychological and social consequences that can influence mental health both during the pandemic and in the future. Therefore, it is believed that psychological factors in connection with the pandemic may lead to a great risk of developing, worsening, and prolonging TMD, since these factors can lead to autonomic responses that result in sleep disorders. This chapter will address the impact of the COVID-19 pandemic on the mental health of TMD patients, focusing on brain changes involving the trigeminal pathway and maladaptive changes in the default mode network (DMN).

Keywords: Anxiety, Coronavirus, COVID-19, Default mode network, Depression, Headache, Mental health, Post-traumatic stress disorder, Psychological factors, Sleep bruxism, Spinal trigeminal nucleus, Temporomandibular joint disorders, Tinnitus, TMD pain, Trigeminal system.

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Jean-Marc Sabatier (Ed.)

INTRODUCTION

Temporomandibular disorder (TMD) is a collective term that involves changes in the temporomandibular joints (TMJ), the masticatory muscles, and the associated tissues [1 - 7], and it is one of the most common chronic orofacial pain syndromes that affect the masticatory system [1]. The etiology is considered multifactorial, since one or more factors may be related to predisposition, initiation, or perpetuation of TMD [2]. There is integration of physical and psychosocial factors [8], and patients with TMD and orofacial pain have a higher prevalence of stressors compared to individuals with no TMD and orofacial pain [9]. Several surveys indicate that TMD is related to mental health conditions [3, 10 - 21], especially anxiety and depression [17, 24]. Post-traumatic stress disorders have also been reported as a contributing factor to TMDs and orofacial pain [14, 15, 21, 25].

The most common signs and symptoms of TMD are orofacial pain, changes in jaw movements, and joint noise [5]. Symptoms that are less specific, such as ear pain, ear fullness, tinnitus, headache, and dizziness may also be present [22]. Some headache conditions may exist in overlap with some painful TMDs, making the diagnosis process more difficult [23]. This overlap suggests a clinical association between these diseases and a possible common pathogenesis of pain for them [26 - 30].

Bruxism has been identified as one of the main factors related to TMD [31], and, although its etiology is not well defined, studies have revealed a connection between bruxism and certain personality traits and psychosocial factors [32 - 35]. Bruxism is a muscular disorder, characterized by the grinding or clenching of the teeth, which can occur during the day (awake bruxism) or during sleep [36 - 43], with prevalence among adults ranging from 9 to 31% [44, 45]. Studies have assessed brain activity during bruxism in patients with TMD, showing decreased neural activation in cerebral areas related to motor and cognitive functions, and abnormalities in DMN during teeth clenching [46 - 48]. Such abnormalities have also been linked to pain rumination [49], post-traumatic stress [50, 51], TMD symptoms (such as tinnitus) [52], and psychological situations (such as fear and anxiety) [53, 54]. Since neurological symptoms such as tinnitus and headache may be present in patients with COVID-19 [55 - 59], patients with TMD and orofacial pain may experience increased stress for believing they are infected, and psychological factors associated with the pandemic can worsen bruxism and pre-existing TMD [60]. Additionally, after the pandemic, the signs and symptoms of pain may be similar to those of post-traumatic stress disorder or syndrome, as well as pain rumination may be present, given the central alterations established [49].

COVID-19 is a new pandemic, which started in late 2019, caused by a virus called SARS-CoV-2 [61 - 63]. However, due to its recent nature, information about this disease is still scarce. The relation between COVID-19, mental diseases, and TMD-related neuropathophysiology of pain should be comprehended, so that specialists can better handle cases of orofacial pain and TMD during and after the pandemic.

TEMPOROMANDIBULAR DISORDER AND OROFACIAL PAIN MECHANISMS

TMDs are defined as a set of musculoskeletal and neuromuscular changes that include numerous anatomical structures in the face and head, which is why diagnosis is complex [1 - 7, 64, 65]. On top of that, the orofacial region has special emotional and psychological significance, given its importance for functions such as drinking, eating, speaking, expressing emotions, and other sensory functions, such as taste and smell [66]. These are highly prevalent conditions worldwide, affecting more women than men [64, 67]. Although these conditions are observed mainly among young adults, surveys have indicated that children and adolescents are also affected [3, 68, 69]. Among the structures involved in TMDs and orofacial pain are TMJs, muscles, ligaments, teeth, periodontium, and all related tissues [5 - 7]. Failure in any of these structures leads to an imbalance of the whole set. TMD can be classified as articular, muscular, or associated with both structures, and the main signs and symptoms are muscular and articular pain, functional limitations, and joint sounds [1].

In 1992, the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) was published — a tool to be used primarily in research and that provided a systematic assessment made up of standardized clinical examination and questionnaires. This tool follows the biopsychosocial model of TMD assessment and classification, consisting of Axis I (physical diagnoses) and Axis II (psychosocial aspects). The inclusion of psychosocial assessments represented a great evolution, as it raised the discussion about the role of these aspects in TMD-related pain, expanding this view to clinical approaches to control such conditions [70, 71]. RDC/TMD has been used in numerous surveys worldwide, as it has been translated into several languages and, over the years, has undergone an extensive accreditation and updating process [72 - 77]. In 2014, the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), an update of RDC/TMD, was published [78]. It also has two axes and its distinguishing feature is that it can be used clinically in addition to research. Axis I is made up of diagnoses of muscular and articular TMD, and TMD-related headache, while Axis II incorporated new confirmed instruments to assess behavior in cases of pain, psychological state, and psychosocial functioning [79, 80]. These tools have been widely used and have

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Jean-Marc Sabatier

Jean-Marc Sabatier is a Director of research at the French CNRS, with Ph.D. and HDR degrees in Biochemistry and Microbiology. He headed several academic research teams (CNRS, INSERM, and University), as well as a combined academic-industry research laboratory devoted to the engineering of therapeutic peptides (ERT62, Marseilles, France). He was also a Director of Research for several French private companies as well as a Canadian public company. He acts as a Consultant for top pharmaceutical and cosmetic companies. Dr. Sabatier works in the field of animal toxins and microbes. He contributed to several books in toxinology and virology and more than 170 scientific articles, 180 communications, and 55 patents in both biology and chemistry. He is a member of 61 Editorial Boards of scientific journals, such as 'Peptides', 'Molecules', 'Antibiotics', and the 'Journal of Biological Chemistry'. He also reviewed articles submitted for publication in >100 international journals and acts as an expert for numerous national and international institutions. He won the 'Citizen of the Year Award' from the Nouvel Economiste (1994) for his work on antivirals. He is a member of a dozen scientific societies, such as the 'American Peptide Society' (charter member), 'European Peptide Society', 'American Society for Microbiology', 'Biochemical Society', and 'New-York Academy of Sciences'.