PHARMACEUTICALS FOR TARGETING CORONAVIRUSES

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CONTENTS

PREFACE

The new coronavirus (2019-nCoV) is part of the group of viruses in a format similar to a crown (Corona), more specifically belonging to the species Betocoronavirus, such as Middle East respiratory syndrome coronavirus (MERS-CoV) and acute respiratory syndrome (SARS). The outbreak was first reported in Wuhan, China, in December 2019, where several cases similar to pneumonia and SARS started to appear with symptoms of fever, cough, and severe respiratory difficulties [1 - 4]. Its origin is still unknown. Some works suggest mutations of the virus in bats or snakes, animals commercialized in the Wuhan market, which have infected humans. The homology similar to the 2019 - nCoV than to your Sequences of Bat SARS-like coronavirus supports the hypothesis that the transmission chain began from the bat and reached the human [5, 6]. It was what happened to the infectious agent that caused COVID-19.

The improvement of drug discovery techniques is fundamental in searching for new therapies that could be selective and effective to combat SARS-CoV-2. Drug discovery approaches are based on ligands (Ligand-Based Drug Design - LBDD) or structures (Structure-Based Drug Discovery - SBDD). Concerning SBDD, it is the main and most evolved technique used for discovering new drugs. The application of SBDD techniques has been improved the pharmacological arsenal against diverse diseases, which allowed to discover innovative treatments, such as inhibitors of HIV-1 proteases. In chapter I, main SBDD techniques (*i.e.*, homology modeling; molecular dynamics and docking; de novo drug discovery; pharmacophore modeling; fragment-based drug discovery; and virtual high-throughput screenings) applied to discover new hit compounds SARS-CoV-2 (COVID-19) will be discussed in detail.

Medicinal plants with a wide range of bioactive compounds, which are exhibiting antiviral activities, are able to provide possible benefits as a preventive and treatment for COVID-19. Rockrose (*Cistus* spp.), lemon balm (*Melissa officinalis* L.), rosemary (*Rosmarinus officinalis* L.), licorice root (*Glyrrhiza glabra* L.), olive leaf (*Olea europea* L.), peppermint (*Mentha piperita* L.), basil (*Ocimum bacilicum* L.), sumac (*Rhus coriaria* L.) and different species of thyme (*Origanum, Thymus,* and *Thymbra*) are important medicinal plants having antiviral activities. Chapter II provides an overview of published scientific information on the development of plant-based antiviral therapeutic agents based on the extensive literature survey. Researchers from all over the world are dedicating themselves to several studies in an attempt to find the best treatment and prevention against the coronavirus. Chapter III addresses the main characteristics of SARS, the main targets and drugs that have achieved excellent results in clinical trials.

With increasing COVID-19 cases globally, it would be too difficult to provide proper treatment even for the severe cases in hospitals. Therefore, the general public is advised to wear the mask, maintain social distancing and use sanitizers. The COVID-19 mild infected patients may be isolated at home and can be taken care of by natural medicines. In chapter IV, an attempt has been made to repurpose all potential natural drugs and natural Ayurvedic formulations that may be beneficial to combat viruses like the SARS-CoV-2 due to their antiviral and immune-modulator properties available under Indian traditional medicine and Chinese traditional medicine system for the effective treatment or prevention of COVID-19.

Peptidomimetics have emerged as a potential class for designing new effective drugs against COVID-19, in addition to lopinavir/ritonavir, in which these drugs are currently being investigated in clinical trials. In chapter V, the authors describe peptidomimetic and peptide-

derived inhibitors of $3CL^{pro}$ from SARS-CoV-2, and also SARS- and MERS-CoV viruses, summarizing all relevant studies based on warhead groups utilization and SAR analysis for all of them to contribute to the development of compounds more selective, effective, and low-costs to combat these emerging viruses.

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CHAPTER 1

Structure-Based Drug Discovery Approaches Applied to SARS-CoV-2 (COVID-19)

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Abstract: Viral diseases have caused millions of deaths around the world. In the past, health organizations and pharmaceutical industries have neglected these diseases for years, mainly because they affected a small geographic population. In contrast, since 2016, several viral outbreaks have been reported worldwide, such as those caused by Ebola, Zika, and SARS-CoV2 (COVID-19). Thus, these have received more attention, leading to increased efforts to search for new antiviral drugs. The SARS-CoV-2 pandemic, already responsible for more than 1,254,567 deaths worldwide, is the greatest example of a virus that has always been present in our society, responsible for small outbreaks in Asian and Arabic countries in 2004 and 2012. But, investments in research to identify/discover new drugs and vaccines were only intensified in 2020, in which only the remdesivir (an FDA-approved drug) was developed to addressCOVID-19 until today. Nonetheless, it has been used in hospitals in the United States and Japan, in emergency cases. Indeed, it justifies greater investments in discovering new alternatives that could save thousands of people. In this context, improving drug discovery techniques is fundamental in searching for new therapies that could be selective and effective to combat SARS-CoV-2. Drug discovery approaches are based on ligands (Ligand-Based Drug Design - LBDD) or structures (Structure-Based Drug Discovery - SBDD). Concerning SBDD, it is the main and most evolved technique used for discovering new drugs. The application of SBDD techniques has improved the pharmacological arsenal against diverse diseases, which allowed the discovery of innovative treatments, such as inhibitors of HIV-1 proteases. In this chapter, main SBDD techniques (*i.e*. homology modeling; molecular dynamics and docking; *de novo* drug discovery; pharmacophore modeling; fragment-based drug discovery; and virtual high-throughput screenings) applied to discover new *hit* compounds SARS-CoV-2 (COVID-19) will be discussed in details.

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Keywords: Drug discovery, Dynamics simulations, Molecular modeling, SARS-CoV-2, Structure-Based Drug Discovery, TMPRSS2, Virtual screening.

1. INTRODUCTION

On December 31st, 2019, an outbreak of pneumonia was reported caused by an unknown etiologic agent in Wuhan, a province of Hubei in China. Thus, with the sporadic number of cases, on January 9th, 2020, the new coronavirus was recognized as the causative agent by the Chinese Center for Disease Control and Prevention (CDC). When it started spreading at an alarming pace to other countries in the world, the new coronavirus (SARS-CoV-2, or COVID-19) was declared a pandemic by the world health organization (WHO) on March 11th, 2020 [1 - 3].

Since its discovery, SARS-CoV-2 has been responsible for several victims worldwide. To date (09/11/2020), there are already 50,266,033 confirmed cases with 1,254,567 deaths [4]. The main symptoms are fever, cough, fatigue, myalgia, and dyspnea. Its transmission occurs mainly through coughing, sneezing, and respiratory droplets [5]. These alarming statistics make research groups from around the world focus on discovering new therapies against this pandemic virus [6]. Advances in drug developments resulted in the repurposing of remdesivir in the United States. However, this drug still does not show the best effectiveness. So, a molecule that could be effective in eliminating SARS-CoV2 from the body is an unmet needed [6, 7].

Currently, biological targets guide the process of discovering new drugs. Then, the structure of a macromolecule is fundamental for this process [8]. Such structures provide valuable information on mechanisms of action and their correlation with biological activity [9]. In addition, information about the biological target and the availability of three-dimensional structures for these therapeutically attractive targets have resulted in several advances in the identification of inhibitors, as well as potential binding sites, contributing to the basis of structure-based drug discovery strategies (SBDD) [10].

In addition, *in silico* methods are increasingly gaining more visibility in the drug development field. These methods are used in SBDD and are related to higher chances of success with less financial cost and less time-consuming [11, 12].

In this context, this chapter will be addressed to the main SBDD techniques (homology modeling; molecular docking and dynamic; pharmacophore modeling; virtual screening and virtual high-throughput screening; fragment-based drug design; and *de novo* drug design) applied for the discovery of new promising compounds against SARS-CoV2.

2. CORONAVIRUSES: HISTORY AND STRUCTURE

Coronaviridae is a family of several groups of viruses responsible for the infection of both animals and humans. From this family, there are seven viruses that can infect humans, being: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV); Middle East Respiratory Syndrome Coronavirus (MERS-CoV); Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); HCoV-OC43; HCoV-KHU1; HCoV-NL63; HCoV-229E [13]. Among these, the first three belong to the genus *Betacoronavirus*, and all of them display high potential for mutability, leading to plasticity and genetic variability, which contributes to their adaptation to different types of hosts [13, 14].

The first discovery of SARS-CoV was around the 1960s [15]. This pathogen is related to flu-like symptoms. However, its progress generates respiratory failure and, in many cases, death since it presents a higher mortality rate [16]. The SARS-CoV is a virus from animal reservoirs (in this case, bats) that can spread to other animals and humans, initially reported in Guangdong (China), in 2002 [16 - 18]. One year later, it spread to Asia and America, affecting 26 nations and causing 8,000 deaths. After its control, other reports were associated with laboratory accidents or transmission from animals to humans [16].

Concerning MERS-CoV, the main reservoir is dromedary camels and bats. These pathogens can infect bat cells through the receptor dipeptidyl peptidase-4 (DPP4), which is similar to the human receptor. The MERS-CoV exhibited widespread exposure in the Middle East and North, as well as in East Africa [17]. This disease was initially identified in 2012, in Saudi Arabia, and it has spread to about 20 countries. Since then, MERS-CoV has been detected in Europe, the Gulf region, and Korea. Since 2016, it is estimated that were infected approximately 1,638 people, of which around 35% were fatal victims [16].

As mentioned in the introduction, a new CoV variant was detected in Wuhan, China (December 2019), giving rise to one of the most significant outbreaks of unknown viral pneumonia. The new SARS-CoV (SARS-CoV-2) is more genetically similar to the SARS-CoV than MERS-CoV. Thus, it could be used information from SARS- and also MERS-CoV to discover new therapies [19, 20].

Deeming the knowledge about the structure and function of the virus, it is possible to model drugs with a focus on each target. In this context, the structure of SARS-CoV-2 is composed of structural and non-structural proteins, being used frequently for the design of new inhibitors. The structural proteins are spike (S) glycoprotein, membrane (M), envelope (E), and nucleocapsid (N) proteins. Among these, S protein is one of the most promising targets in drug discovery for SARS-CoV-2. This protein is related to viral entry by recognition of the

CHAPTER 2

Potential Antiviral Medicinal Plants against Novel SARS-CoV-2 and COVID-19 Outbreak

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Abstract: Considering the significant worldwide threat of the Novel Corona Virus Disease 2019 (COVID-19), it is urgently needed to develop efficient prevention and treatment approaches in order to reduce the prevalence rate and mortality of the disease. Even though numerous experimental and clinical studies have been currently conducted for development of drug and vaccine througout the world, and some partially effective vaccines and chemical drugs have been developed against COVID-19. Herbal and dietary plants, including fruits, vegetables, herbs, spices, cereals, and edible tubers/roots, can play a significant role in enhanging the immune system and how to increase our defense barriers against virus-related diseases. Accordingly, medicinal plants with a wide range of bioactive compounds, which exhibit remarkable antiviral activities, can be used as a preventive treatment and cure for COVID-19. In order to combat SARS-CoV-2, rockrose (*Cistus* spp.), lemon balm (*Melissa officinalis* L.), rosemary (*Rosmarinus officinalis* L.), licorice root (*Glyrrhiza glabra* L.), olive leaf (*Olea europea* L.), peppermint (*Mentha piperita* L.), basil (*Ocimum bacilicum* L.), sumac (*Rhus coriaria* L.) and different species of thyme (*Origanum, Thymus* and *Thymbra*) are important medicinal plants that exhibit valuable antiviral activities. Since medicinal and aromatic plants are a worldwide hot topic, the aim of the current review was to provide an overview of the development of plant-based anti-coronavirus agents to the researchers based on an extensive literature survey.

Keywords: Antiviral, Bioactive compounds, *Cistus* spp., Coronavirus, COVID-19, Immune system, Lemon balm, Licorice root, Medicinal plants, *Melissa officinalis* L., *Ocimum bacilicum* L., Olive leaf, Outbreak, Peppermint, Pharmaceutical industry, Phytochemicals, *Rhus coriaria* L., Rockrose, Rosemary, Therapeutics.

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1. INTRODUCTION

Throughout history, pandemics of large-scale outbreaks of infectious diseases such as Cholera, Ebola, Bubonic Plague, AIDS (acquired immunodeficiency syndrome), Influenza, SARS (severe acute respiratory syndrome), MERS (Middle East Respiratory Syndrome), and currently COVID-19 (new type coronavirus, causative agent 2019-nCoV or SARS-CoV-2) have had a major impact worldwide. The Corona Virus Disease 2019 (COVID-19) has had similar outbreaks to other viral diseases because of its global spread, social and economic response, however, the recent coronavirus outbreak is different from other occurrences. It has different biological properties, cell surface proteins, and mechanisms of infection [1 - 4].

Coronaviruses (CoVs) belong to the family of Coronaviridae, Arteriviridae, Roniviridae and Mesoniviridae families. Of which, Coronaviridae is the largest family and includes the subfamily of Coronavirinae, which is now classified into four main genera including alpha (α)-coronavirus, beta (β)-coronavirus, gamma (γ)-coronavirus and delta (δ)-coronavirus, according to the 10th report on virus taxonomy from the International Committee on Taxonomy of Viruses (ICTV). α-coronaviruses and β-coronaviruses infect a variety of host cells and can cause life-threatening pneumonia in humans and some animals such as feline, porcine, canine, mice, bovine, bat and rodent, while γ-coronavirus and δ-coronavirus are specific of birds, but some of them can also infect other organisms [4 - 6].

CoV is an enveloped virus group that carries single-strand RNA (ribonucleic acid) genome, capable of infecting humans and a wide variety of animal species. This group of viruses, especially causing upper respiratory infections, lead symptoms that present with a sore throat, dry cough, runny nose, weakness, and fatigue. In coronavirus infections, the symptoms occur in the form of colds or flu; the virus infects the ciliated epithelial cells in the nasopharynx through the aminopeptidase N receptor or sialic acid receptors and leads to the development of damage to the epithelial cells as the virus multiplies. In addition, chemokines and interleukins released from the cells cause the development of local illnesses in the patients. In the following process, the virus can pass to pneumocytes, blood, urine (up to 2 months), and in some cases to feces [3, 7, 8].

Based on the ICTV, FECV (Feline Enteric Coronavirus) and FIPV (Feline Infectious Peritonitis Virus), the porcine TGEV (Transmissible Gastro- Enteritis Virus), Porcine PEDV (Epidemic Diarrhea Virus), PRCoV (Porcine Respiratory Coronavirus), CCoV (Canina Coronavirus), and human coronaviruses (HCoV-229E and HCoVNL63) are of α-coronaviruses. Betacoronaviruses also compromise Murine coronavirus (MHV) and Bovine Coronavirus (BCoV), and

human coronaviruses (HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2 Interestingly, recent studies have shown that the new human CoV, namely SARS-CoV-2, shares high genome sequence similarity (almost 79.5%) with SARS-CoV, and similar to SARS-CoV, the new human CoV recognizes ACE2 (angiotensin-converting enzyme 2) cellular receptor to enter host cells. In addition to that, it has a similar genomic structure as SARS-CoV and MERS-CoV [2, 9 - 11].

Even though the history of CoVs began in the 1940's, the first human CoVs subsequently named as (i) human CoV 229E (HCoV-229E) and (ii) HCoV-OC43, were reported in the 1960's. After that, the virologist tried to identify the general structure of CoVs, as well as-replication and pathogenesis. The studies among the virologist provided to the discovery of other new human coronaviruses such as (iii) HCoV- Hong Kong University 1 (HKU1), (iv) HCoV-NL63, (v) severe acute respiratory syndrome (SARS)-CoV and (vi) the Middle East respiratory syndrome (MERS)-CoV [2, 9, 12]. Among these coronaviruses, SARS-CoV was identified as a global outbreak in 2003, and it had affected 8422 people in 32 countries, with a mortality rate of 10-15% [3, 13]. Then, almost after ten years, another highly pathogenic coronavirus MERS-CoV epidemic emerged in Middle Eastern countries in 2013. Although the major MERS-CoV pandemic has happened in the Republic of Korea, it was observed worldwide at any age of people with a fatality rate of 39% [12, 14]. Following this outbreak, the novel coronavirus outbreak, namely 2019-nCoV or COVID-19 emerged in Wuhan State, Hubei Province, China, in December 2019. It has spread to many countries and territories, United States (US), Spain, Italy, France, Germany, the United Kingdom, China, Iran, Turkey, Belgium and Netherlands are among the hardest hit countries. Since, it has infected many people and caused a high mortality rate in a short period, the World Health Organization (WHO) has declared the outbreak of the new coronavirus as a pandemic. As of 19 November 2021, more than 255,324,963 confirmed cases of COVID-19 have been reported in more than 180 countries and territories, resulting in approximately 5,127,696 deaths all around the world [15, 16]. Moreover, the number of infected patients with COVID-19 and death from this virus are alarmingly increasing day by day. Due to its rapid infection ability from person to person and high mortality rate, it has become vital to find efficient and accurate therapy strategies to urgently combat this disaster [17, 18]. Thus, scientists have been racing to understand the different coronavirus diseases in order to discover possible therapy strategies including drugs, therapeutic antibodies, cytokines, nucleic acid-based therapy, vaccines to treat and prevent coronavirus infections. Among the given strategies, researching effective antiviral drugs, which may be appropriate to cure the COVID-19, have apparently been the most certain option for immediate treatment. Nevertheless, no specific drug has been studied or made available for COVID-19 cases and clinical trials, as well as

CHAPTER 3

Infections Caused by SARS: Main Characteristics, Targets and Inhibitors

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Abstract: SARS-coronavirus (SARS-CoV) originated in China from 2002 to 2003 and caused a global outbreak with 8098 cases and 774 confirmed deaths. More than 15 years later, in less than a year, the new coronavirus (2019-nCoV) has infected more than 44 million people and killed more than 1 million. The COVID-19 pandemic has brought serious consequences for several countries and a worldwide alert about coronaviruses. Severe acute respiratory syndrome (SARS) is an emerging infectious viral disease characterized by severe clinical manifestations of the lower respiratory tract that lead to severe lung damage and the spread of the virus to several other organs. Phylogenetic analyzes demonstrate that SARS-CoV-2 shares a 79% identity with SARS-CoV, and just as there was no effective treatment against SARS-CoV, it does not yet exist against SARS-CoV-2. However, researchers from all over the world are dedicating themselves to several studies in an attempt to find the best treatment and prevention against the coronavirus. Thus, this book chapter addresses the main characteristics of SARS, the main targets and drugs that have achieved excellent results in clinical trials.

Keywords: Drugs, SARS, SARS-CoV, Sar-CoV-2, Target.

1. INTRODUCTION

Coronaviruses (CoVs) are RNA viruses that cause respiratory and enteric diseases with variable pathogenicity in humans and animals. All CoVs are known to infect humans are zoonotic, or of animal origin, and many believe they originate from host bats [1, 2]. Due to the large size of the genome (the largest non-segmented RNA viral genome), single-stranded and positive sense of about 26–32 kb in size, frequent recombination and high genomic plasticity, CoVs are prone to transmission between species and are able to adapt quickly to new hosts [2, 3].

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Severe acute respiratory syndrome (SARS), which emerged as a pandemic in 2002 and 2003, was caused by Severe acute respiratory syndrome coronavirus (SARS-CoV), a virus previously unknown [4, 5]. This virus was first isolated in 2003 from samples from three SARS patients. According to the World Health Organization (WHO), SARS has infected more than 8,000 people and caused at least 813 deaths [6, 7].

SARS-CoV has been identified as a clinical entity in which patients have a fever, dry cough, dyspnoea, headache and hypoxemia. Typical laboratory findings are lymphopenia and slightly elevated aminotransferase levels. Death can result from progressive respiratory failure due to alveolar damage caused by an infectious agent transmitted from human to human [8].

The pathological features available for SARS-CoV infections were mainly obtained at autopsies. The predominant visceral macroscopic were changes in fatal cases of SARS - CoV mainly in edematous lungs with increased gross weight and multiple areas of congestion, increased lymph nodes in the pulmonary hiluses and in the abdominal cavity, as well as decreased spleen size and reduced spleen weight [9, 10].

A large number of SARS-CoV particles and genomic sequences have been detected in circulating lymphocytes, monocytes and lymphoid tissues, as well as in epithelial cells of the respiratory tract, intestinal mucosa, epithelium of renal distal tubules, neurons in the brain and macrophages residing in tissues that reside in different organs [11]. The therapeutic agent effective against SARS was unavailable at the time of the initial outbreak. Fortunately, SARS has been successfully contained, and no SARS outbreaks have been reported since 2004 [4].

An outbreak of pneumonia with unknown cause was reported in Wuhan, Hubei province, China, in December 2019, associated with the Huanan Seafood Wholesale Market [12]. The causative agent of the outbreak was identified by the WHO as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), producing the disease called coronavirus disease-2019 (COVID-19) (13). SARS-CoV-2 shares 96.3%, 89% and 82% of nucleotide similarity with the bat CoV RaTG13, SARS-like CoV ZXC21 and SARS-CoV, respectively, which confirms its zoonotic origin, based on the analysis phylogenetics [13 - 15]. Human-t--human transmission has been confirmed even in asymptomatic carriers.

The virus has spread to at least 219 countries and territories and in October 2020, the global epidemiological situation is over 42 million cases and 1.1 million deaths reported globally, with massive global increases in the number of daily

cases with more 2.8 million new cases and nearly 40,000 new deaths reported in the past few days [16].

2. ORIGIN AND EPIDEMIOLOGY

At the beginning of the SARS epidemic, most patients had animal exposure rates before developing the disease. Subsequently, the causative agent of SARS was identified, SARS-CoV and / or anti-SARS-CoV antibodies were found in palm civets (Paguma larvata) and animals handled in a market [17 - 20]. However, research using breeding and wild civets revealed that the SARS-CoV strains found in market civets were passed on to them by other animals [21, 22].

Research has also identified the coronavirus in zoonotic reservoirs, including horseshoe bats (genus Rhinolophus), Himalayan palm civets (*Paguma larvata*) and raccoon dogs (*Nyctereutes procyonoides*), and determined that the virus that infected human hosts is from southern China, in Guangdong province [2, 7 - 9].

Subsequent studies have shown that wild horseshoe bats (Family Rhinolophidae), which can also be found in LAM in China and served in some Chinese restaurants in Guangdong, China, have detectable levels of antibodies against SARS-CoV, suggesting a bat origin for the SARS-CoV [22].

The evolutionary relationship between coronavirus and bats was proposed, in which the ancestor for SARS-CoV first spread to bats of the Hipposideridae family, then to Rhinolophidae and then to palm civets and, eventually, to humans [23].

In 2013, two new SARS-like CoVs were isolated from Rhinolophus bats in China, and these viruses showed a high relationship with SARS-CoV of all bat coronaviruses [24]. ORF8 analysis of SARS-identical CoVs in bats suggests that Chinese horseshoe bats are the natural reservoirs of SARS-CoV, these viruses are identified by a set of unique accessory open reading structures (Open Read Frame - ORFs) that are located between the M genes and N [25].

According to their antigenic and genetic characteristics, CoVs are classified into three groups. The main group of CoVs comprises Porcine Transmissible Gastroenteritis Virus (TGEV), Feline Coronavirus (FCoV), Canine Coronavirus (CCoV), HCoV-229E and Porcine Epidemic Diarrhea Virus (PEDV). The second group consists of murine hepatitis Virus (MHV), Bovine Coronavirus (BCoV), HCoV-OC43, Swine Hemagglutinating Encephalomyelitis Virus (HEV), Rat Coronavirus (RtCoV) and Equine Coronavirus (ECoV). The third group is formed by Avian Infectious Bronchitis Virus (IBV), Turkey Coronavirus (TCoV) and Coronavirus Pheasant [26]. This subfamily is formed by four genera,

CHAPTER 4

Natural Sourced Traditional Indian and Chinese Medicines to Combat COVID-19

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Abstract: The corona virus disease (COVID-19) was started in Wuhan, China, in late 2019. It is caused by a novel strain of severe acute respiratory syndrome corona viruses (SARS-CoV-2) that has become pandemic on March 11, 2020 and endangered the existence of human beings on the earth as the infection has been spreading in mass population day by day within a few months with a high killing rate. The COVID-19 pandemic has pushed the modern health care system of developing and developed countries to their limits for its effective management and control since the drug discovery process is a long journey and challenging task and there is no specific small molecule chemotherapeutics to combat this novel coronavirus. Hence, the existence of human life is a great challenge. Mother Nature has played an important role to combat many pandemics that arrived in past centuries in absence of modern medicines. Nature has been a source of many natural drugs derived from plants' secondary metabolites which may be used to combat COVID-19. Natural sourced traditional Indian and Chinese medicines alternative therapy should be prioritized in combination with modern medicines to combat COVID-19. With rising COVID-19 cases globally, it would be too difficult to provide proper treatment even for the severe cases in hospitals. Therefore, the general public is advised to wear the mask, maintain social distancing, and use sanitizers. The COVID-19 mild infected patients may be isolated at home and can be taken care of by natural medicines. In this chapter, an attempt has been made to repurpose all potential natural drugs and natural Ayurvedic formulations that may be beneficial to combat viruses like the SARS-CoV-2, due to their antiviral and immune-modulator properties available under Indian traditional medicine and Chinese traditional medicine system for the effective treatment or prevention of COVID-19.

Keywords: COVID-19, Drug repurposing, Natural formulations, Traditional Chinese medicines (TCM), Traditional Indian medicines (TIM).

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Luciana Scotti and Marcus T. Scotti (Eds.)

1. INTRODUCTION TO INDIAN AND CHINESE TRADITIONAL MEDICINE

In the current 21st century, when the whole world is fighting a tough and decisive battle against COVID-19 caused by a novel coronavirus, natural products and their derivatives have potential activities to combat this pandemic [1, 2]. Since the beginning of 2020, new anti COVID-19 drug discovery strategies based on natural products and traditional medicines are evolving as an alternative option till specific anti COVID-19 drugs and vaccines are introduced in the global market to eliminate novel coronavirus [3].

According to the World Health Organization (WHO), the traditional medicine system includes a diversity of health practices, approaches, knowledge, and beliefs that incorporates plant, animal, and/or mineral-based medicines, spiritual therapies, manual techniques, and exercises, which are applied singly or in combination to maintain well-being and to treat or prevent the illness [4]. India, one of the ancient civilizations of the world, has the oldest heritage of the traditional medicine system, nurtured between 2500 B.C and 500 BC. The Sanskrit meaning of Ayu is life and Veda is knowledge or science [5]. Medicinal plants play a major role and constitute the backbone of traditional medicine. The Indian materia medica includes about 2000 drugs that are derived from India's different traditional systems, hence, Indian medicinal plants and other traditional medicines can be considered as a new option to overcome the viral transmission of COVID 19 [6]. Similarly, Traditional Chinese medicine (TCM), is one of the oldest continuously surviving traditions. The TCM is a system of healing that developed in China about 3000 years ago and includes natural herbal medicines used for maintaining good health and treating diseases in Chinese communities and has been adopted recently by other countries worldwide. In the year 2020, the use of TCM has become very popular in China and other parts of the world due to its effective utilization in combating COVID-19 [7]. At this time, in the absence of any specific anti COVID drug, all countries, including India, have to join hands together to fight COVID-19 by practicing precautionary measures such as regular hand washing, wearing of masks, and social distancing to prevent the attack of COVID-19 infection. In this study, an effort has been made to review and enlist the antiviral drugs and formulation of natural origin available and reported in Indian and Chinese traditional systems to combat COVID-19.

In December 2019, the sudden emergence of novel coronavirus (2019-nCoV) was observed by the world. It has been erupted in China Wuhan, Hubei Province, and spread across China and beyond [8]. On January 30, 2020, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (PHEIC) [9]. On February 12, 2020, WHO named the

disease caused by the novel coronavirus Coronavirus Disease 2019, (COVID-19) [10].

The 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as it is now called [11] has its history began back in the late 1960s when virologist Tyrrell and Bynoe found that they could passage a virus named B814 obtained from the respiratory tract of an adult with a common cold [12]. As a leading virologist, Tyrrell worked with the human strains, and several animal viruses like bronchitis virus, hepatitis virus demonstrated their same morphology under an electron microscope [13, 14]. This new group of viruses was named "coronavirus". Coronaviruses are enveloped positive-sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike-like projections on their surface, giving them a crown-like appearance under the electron microscope; hence the name "coronavirus". The main targets of the SARS-CoV-2 are spike, envelope, membrane, nucleocapsid, and viral genome, which are responsible for the virulence while diffusing into the host cell by binding the viral spike with the human ACE 2 receptor [15] (Fig. **1**).

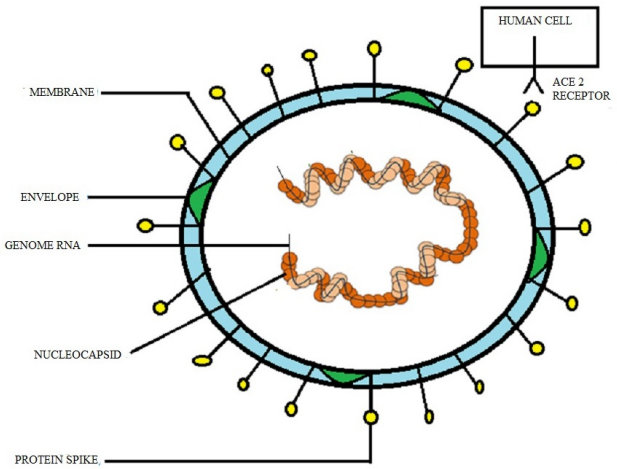

Fig. (1). Structure of novel coronavirus virion and its binding site in human body [15, 16].

Coronaviruses, having a total of 39 species under the broad realm of Riboviria, belong to the family Coronaviridae, suborder Cornidovirineae and order Nidovirales. Human coronavirus (HCoV-HKU1), SARS-CoV, SARS CoV-2, and Middle East respiratory syndrome coronavirus (MERS-CoV), belong to the betacoronavirus genus [16, 17] of them SARS CoV-2 is very dangerous because of its high killing rate of the human population, which directly hit the socioeconomic movement of the world.

CHAPTER 5

Peptidomimetic and Peptide-Derived Against 3CL^{pro} from Coronaviruses

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Abstract: SARS-CoV-2 is an RNA virus responsible for causing pandemic COVID-19, which has taken on unprecedented proportions so far in global health and economic aspects. In this context, the search for effective drugs against SARS-CoV-2 has become a priority for the global scientific community, where the chymotrypsin-like picornavirus 3C-like protease (3CL^{pro}, which is also named as main protease (M^{pro}), or only 3C) is a promising druggable target since it is crucial for the process of viral replication. Several 3CL^{pro} inhibitors have been recently reported in the literature. Thus, peptidomimetics have emerged as a potential class for designing new effective drugs against COVID-19, in addition to lopinavir/ritonavir, in which these drugs are currently being investigated in clinical trials. In this chapter, we describe peptidomimetic and peptide-derived inhibitors of 3CL^{pro} from SARS-CoV-2, and also SARS- and MERS-CoV viruses, summarizing all relevant studies based on warhead groups utilization and SAR analysis for all of them in order to contribute to the development of compounds more selective, effective, and low-costs to combat these emerging viruses.

Keywords: 3CL^{pro} inhibitors, Drug Design, MERS-CoV, Peptidomimetics, SARS-CoV, SARS-CoV-2.

1. INTRODUCTION

Coronavirus (CoV) refers to enveloped viruses belonging to the family *Coronaviridae* (subfamily: *Coronavirinae*; order: *Nidovirales*), which is responsible for causing potential severe infectious processes in the human respiratory tract [1, 2].

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Two serious epidemics were caused by CoV, being *Middle East Respiratory Syndrome-coronavirus* (MERS-CoV), Arabian Peninsula, causing a total of 740 deaths, and 2,123 cases, in 2014. Besides, *Severe Acute Respiratory Syndrome-coronavirus* (SARS-CoV) was responsible for infecting 8,500 individuals, leading to 800 deaths in Guangdong province of China, between 2002-2003 [3 - 5].

Recently declared a pandemic by WHO (March 11th, 2020), COVID-19 is caused by the SARS-CoV-2 (previously called 2019-nCoV) [6]. Initially, it was reported on December 8th, 2019, in Wuhan, Huabei, China [7 - 9], causing severe respiratory complications. So far, this new-CoV has infected more than 246 million individuals worldwide, causing more than 5 million deaths, up to November 3rd 2021 [10].

Even in the third outbreak caused by a coronavirus, there is still no approved treatment or selective antiviral agents to combat this virus, nor approved vaccines [11 - 14]. Thus, current therapy involves treating symptoms, as well as providing oxygenation to the affected individuals, in addition to protective methods to avoid viral transmissions, such as wearing masks, hand hygiene, and social distancing [15, 16].

Medicinal chemistry has concentrated strategies for the development of bioactive compounds against the new coronavirus targeting enzymes [17, 18], in special the chymotrypsin-like picornavirus 3C-like protease (3CL^{pro}, also called main protease (M^{pro}), or only 3C), which emerges as the main druggable target from SARS-, MERS-CoV, and SARS-CoV-2 [17 - 22].

This protease (corresponding to nsP5) is directly responsible for the cleavage of the pp1a and pp1ab proteins, thus exercising a primordial function for controlling the viral cycle of replication [23 - 25]. Moreover, the genome sequence of SARS-CoV-2 3CL^{pro} is closely similar to the same protein from SARS-CoV [26, 27].

The utilization of peptide-based drugs (also named peptidomimetics) has been widely related to the design of bioactive compounds since this chemical class is involved in several regulatory processes in the human organism [28, 29]. Furthermore, endogenous peptides tend to demonstrate a strong binding with enzymatically active sites [30, 31].

In this context, this chapter summarizes strategies for developing peptidomimetics against 3CL^{pro} from MERS-, SARS-CoV, and SARS-CoV-2. We aim to demonstrate some warhead groups used in the design of these inhibitors, as well as discuss SAR analysis involving the most promising compounds, thus providing valuable information to assist in the development of new anti-virus drugs against this global emergency.

2. CHEMISTRY ASPECTS OF PEPTIDOMIMETICS

Peptides are intrinsically related to several physiological mechanisms in humans, in order to promote regulation of functions in the immune, digestive, defense, reproductive, respiratory, circulatory systems, in addition to metabolism and reproduction. Thus, at least 60 peptides have been described in the literature for therapeutic use in different clinical stages, being reported as inhibitors against HIV protease, hepatitis C virus (HCV), antimicrobial, treatment of dry eye syndrome (DED), among other activities, as described in Fig. (**1**) [31 - 35].

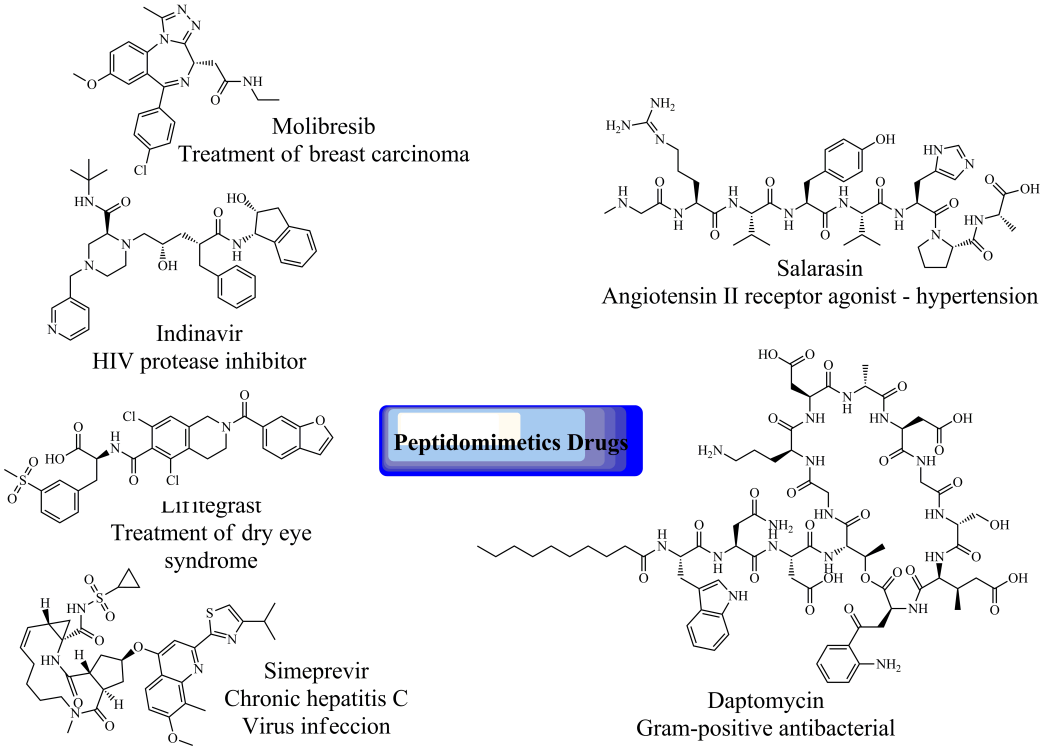

Fig. (1). Peptide-based drugs and their biological applications.

In 2010, four peptide drugs were responsible for US$ 1 billion in global sales, demonstrating the therapeutic potential from this drug design approach [36]. However, the peptide-based drug design still has a significant disadvantage in some pharmacokinetic aspects due to their high molecular mass can result in deficient absorption since there is no specific transport system for them. Also, these compounds present limited stability in toward proteolysis from the gastrointestinal system and serum [30, 33, 37].

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Z

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Marcus T. Scotti

Prof. Marcus Tullius Scotti studied chemical engineering at Universidade de São Paulo (USP - São Paulo University) and finished his degree in 1999. Later, he worked for four years in a brazilian electronics and telecommunications services company called Gradiente. At the same time, he started to specialize in the field of Industrial Administration at the University of São Paulo. After that, he started post-graduation in organic chemistry at the University of São Paulo in 2003, and finished his Master's in 2005 and Ph.D. in 2008. In January 2009, he moved to João Pessoa and started to work as a Professor of Organic Chemistry at the Universidade Federal da Paraíba (Federal University of Paraíba), Brazil. At the beginning of 2014, he completed his Post-doc in cheminformatics at the Universidade Nova de Lisboa, Portugal, Prof. Marcus' research interests lie in the area of chemistry of the natural products, acting on the following subjects: QSAR, Virtual Screening, molecular descriptors and chemotaxonomy using cheminformatics methods using several statistic tools and machine learning algorithms.