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An alternative approach to minimize the risk of coronavirus (Covid-19) and similar infections

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Abstract. **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new strain that was discovered in 2019 and has not been previously identified in humans. On December 31st 2019 World Health Organization (WHO) was informed of a cluster of cases with pneumonia of unknown origin from Wuhan City, Hubei province of China. The WHO announced in February 2020 that COVID-19 is the official name of the coronavirus diseases. A total of 519,899 confirmed cases with 23,592 deaths linked to this pathogen as on March 27, 2020 have been reported. Due to increasing number of infected people across the continents and huge loss to human life, the WHO has declared the novel COVID-19 outbreak a pandemic. A pandemic is defined as the "worldwide spread" of a new disease. Currently, no COVID-19 specific treatments have been approved by the United States Food and Drug Administration (US-FDA). However, the current treatment options include hydroxychloroquine, tocilizumab, remdesivir, lopinavir-ritonavir (Kaletra®), and nitazoxanide. In recent past, some natural herbal compounds have demonstrated encouraging anti-viral properties. This article attempted to summarize available information on the reported anti-viral activity of some natural products.**

Key Words:
Coronavirus, COVID-19, Pandemic, Anti-viral natural products.

Introduction

Infectious diseases are a major global problem and are still causing substantial morbidity and mortality despite considerable developments in medical sciences. In particular, advancement in anti-viral therapy is hampered by the emergence of mutants capable of overcoming the effects of drugs that target viral components[1]. In addition, increased global travel and rapid urbanization, infectious outbreaks triggered by emerging and re-emerging viruses pose a vital threat to public safety, especially in the absence of effective anti-viral therapies and preventive vaccines[2,3]. For several years, medicinal plants have been used in different indigenous health schemes as well as traditional medicines for treating diseases[3]. Naturally occurring/herbal medicine provides a wide variety of natural products, which can serve as an ancillary guide to unlocking the many mysteries behind human illnesses[4,5]. According to a report by the WHO, 80% of the population in developing countries relies on conventional plants for health needs[5-7]. With the resistance of microorganisms (bacteria, viruses, and parasites) to traditional antimicrobial therapy, alternative therapies are being re-explored at a growing pace, particularly from herbal sources[7]. In fact, assessment of possible antiviral activity of various natural resources has gained a remarkable rate with the emergence and re-emergence of new viruses in the light of the advancing technological resources available[3,5,8]. A variety of herbs have been investigated, and their effects against viral infections have been identified[3]. Amidst the mounting global concerns about the COVID-19 outbreak, an understanding and knowledge of the natural products with anti-viral properties is essential for providing an alternative management option for COVID-19. The objective of this mini-review is to gather and highlight the information on different natural products with anti-viral properties in general and on COVID-19 in particular.

Methodology

A systematic literature searches of PubMed and Embase (Elsevier) databases was performed on March 12-20, by means of keywords: "Coronavi-

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rus", "COVID-19", "2019-nCoV and anti-viral natural products". Taking in consideration the importance of the theme and to enhance the sensitivity of the search, a classical literature search was conducted using the similar keywords on Google Scholar to hit the published articles in recent past. Additionally, the publication database of WHO on novel Coronavirus was searched for potentially relevant publications (www.who.int). With consideration of the date of the first confirmed reports of COVID-19, we restricted our search to articles published in 2020. Because of the large number of hits identified, the Google Scholar search was restricted to papers' titles. However, no additional restrictions were applied in the PubMed or Embase search.

COVID-19 Overview

Viral infections have been linked with many hard to treat diseases and complex syndromes. Coronaviruses (CoV) is from the genus Coronavirus of Coronaviridae. CoVs are single stranded RNA (SsRNA) viruses typically found with spike like projections on its oval surface visible under electron microscope hence the name coronaviruses (CoV). They have positive polarity of 27-32 kb, SsRNA of 29,903 bp length and size range from 80-160 nm[9]. SARS-CoV-2 (COVID-19) has weak resistance; 56°C for 30 min, ethanol (75%), disinfectants containing chlorine and peracetic acid can inactivate SARS-CoV-2[10-12]. For entry into the host cells, SARS-CoV-2 uses the SARS-coronavirus receptor and the angiotensin-converting enzyme 2 (ACE2). ACE2 is a strongly expressed surface molecule in AT2 lung cells, along with oesophageal upper epithelial cells and ioleum and colon absorptive enterocytes, suggesting that the digestive system and respiratory systems are possible routes for SARS-CoV-2[13,14]. In Asians, the expression level of ACE-2 is slightly greater than in Europeans and Americans, and ACE-2 in male cells is greater than in female cells, which may partly explain the occurrence rate of novel coronavirus pneumonia in males and Asia[15,16]. SARS-CoV has very high mutation rate and this zoonotic pathogens affecting humans as well as many animal species. The clinical features of CoV infection range from being asymptomatic to need of hospitalizations in intensive care unit. The infection mainly affects respiratory, hepatic, neurological and gastrointestinal systems[17]. Till date only four types of coronaviruses NL63, HKU1, OC43 and 229E are in circulation in humans and usually cause mild respiratory disorders[18].

In December 2019, many people from Wuhan in Hubei Province in China started visiting hospitals complaining about severe pneumonia of unknown origin[19]. Most of the early cases were reported to have a common origin to the Huanan market which deals with trade of sea foods and live animals. On 31st December 2019, China informed the outbreak to WHO and on 1st January Chinese government shut down the Huanan sea food market. On 7th January it was reported that virus has very high homology with bat coronavirus and is similar to SARS-CoV[18,19]. As the number of patients with CoV like symptoms was on rise which included the population not exposed to the live animal market, it became evident that human-to-human transmission was occurring[20]. As of March 27, 2020, a total of 519,899 confirmed cases of COVID-19 and 23,592 deaths have been declared (www.worldometer.info/corona; www.who.int).

The current data shows major transmission routes are droplets transmission, contact transmission, and aerosol transmission. The incubation period of COVID-19 is reported to be 1–14 days. Fever, cough and shortness of breath may appear 2-14 days after exposure. COVID-19 diagnosis is dependent on a detailed history of touch and transport, and accurate laboratory tests. Nucleic acid or viral gene checks by polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), High-throughput sequencing and computed tomography (CT) scan of the lungs are the main diagnostic methods. Test results contain nasopharyngeal swab, sputum, lower respiratory tract secretions, blood, and feces. The most popular specimens are nasopharyngeal swab, but its positive detection rate is less than 50%. Repeated identification is required to render the positive rate higher. The positive levels of bronchoalveolar lavage fluid was strong but owing to an elevated risk of cross-infection, it is not appropriate for most patients[21,22].

COVID-19 vaccine is currently missing. Current treatment methods are essentially supportive and symptomatic. In addition, there is no approved specific therapy available for COVID-19 infection. However, several treatment protocols have been advocated which include using hydroxychloroquine, tocilizumab, remdesivir, lopinavir-ritonavir (Kaletra®), and nitazoxanide, (www.med.umich.edu/asp; accessed March 21, 2020). Antibiotics and anti-fungal are needed only if co-infections are suspected or identified in infected patients[18]. Therefore, there is a crucial need to develop new antivirals that are highly effective and cost-effective for the treatment and control of viral infections. The

goal of this search was to identify published reports on phytochemicals identified for their role in managing of viral infections.

Natural Therapeutic Approach

The use of natural products and phytomedicine continues to grow fast around the world with many people nowadays reverting to such remedies in different national healthcare settings for treatment of various health challenges[23]. Herbal phytoconstituents have been found to be effective in reducing infectious conditions and were the only treatments available before antibiotics were introduced. In particular, herbal medicinal products provide a rich tool for the production of novel antivirals. Identifying the antiviral mechanisms of these natural products has elucidated on where and how they interact/interrupt with the viral life cycle, including viral input, replication, assembly and release; also, as virus-specific interactions. Cheng at al[24] have reported naturally occurring triterpene glycosides (saikosaponins A, B, C, and D) isolated from medicinal plants such as *Heteromorpha spp.*, *Bupleurum spp*, and *Scrophularia scorodonia*, exert antiviral activity against HCoV-22E9. These natural compounds were found to be effectively preventing the early stage of HCoV-22E9 infection through affecting viral attachment and penetration. Extracts from *Artemisia annua, Lycoris radiate, Pyrrosia lingua and Lindera aggregata* have also been reported to display anti–SARS-CoV effects from a screening analysis using huge number Chinese medicinal herbs[25]. Natural inhibitors such as the nsP13 helicase and 3CL protease have been identified and myricetin, scutellarein, and phenolic compounds from *Isatis indigotica* and *Torreya nucifera* against the SARS-CoV enzymes[26-28]. The aqueous extract from *Houttuynia cordata*, which has been found to display different antiviral mechanisms against SARS-CoV that include inhibiting the viral 3CL protease and blocking the activity of viral RNA-dependent RNA polymerase[29] (Figure 1). Cinatl et al[30] have reported that glycyrrhizin elicited a significant antiviral activity against SARS coronavirus. *Nigella sativa* (Black seed) of the family Ranunculaceae emerges as natural product with potential pharmacological activities including antidiabetic, anticancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, bronchodilator, renal and gastro-protective, and antioxidant properties[31-33]. It is indicated that these effects are attributed to the presence of thymoquinone, which is a significant bioactive portion of the essential oil of *Nigella sativa*[32]. Furthermore, the antiviral activity of thymoquinone and black seed fixed oil against avian influenza virus (H9N2) 35 and murine cytomegalovirus infection model 36 has been reported[34,35]. *Ginger, Zingiber* officinale, is a widely used medicinal plant, which

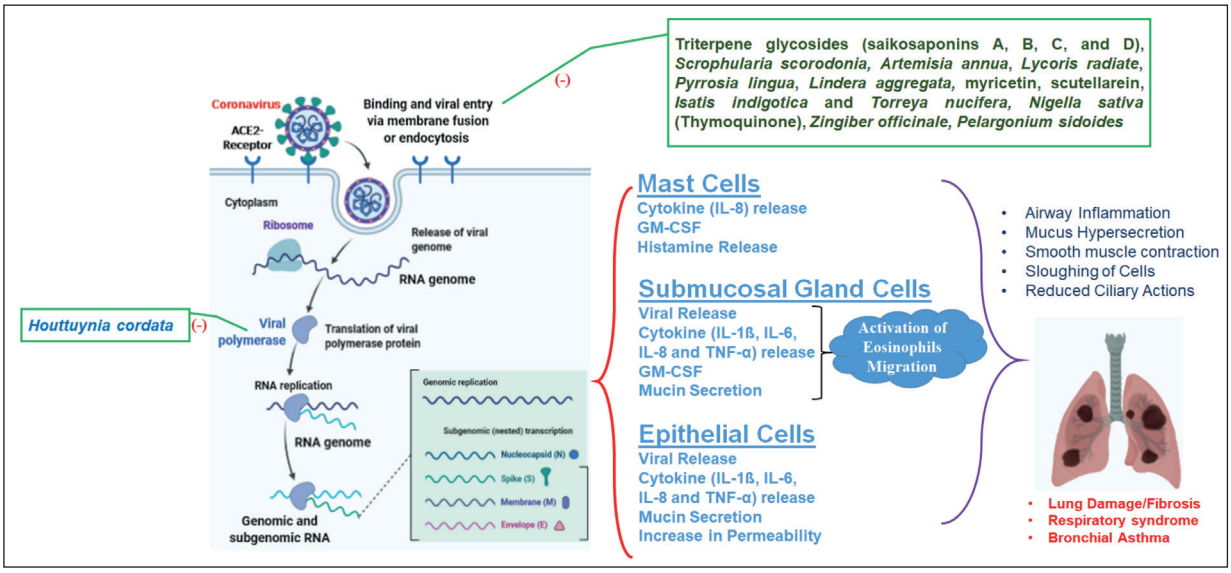

Figure 1. Schematic illustration of a viral transmission (Corona virus) replication cycle and infection on the pathogenesis of viral infection induced respiratory syndrome/lung damage and the natural compound inhibitory effects on viral infection. IL: interleukin, TNF: tumor necrosis factor, GM-CSF: granulocyte-macrophage colony stimulating factor, (-): inhibition. Source: https://biorender.com. Accessed on 18th March 2020.

has been found active against Human Respiratory Syncytial Virus (HRSV)-induced plaque formation on the epithelium of the airways through blocking viral attachment and internalization[36]. Another traditional herb known as *Pelargonium sidoides*, native to South Africa, has been used by local communities for centuries as herbal treatments for respiratory infections. Interestingly, an extract of *Pelargonium sidoides* reduces rhinovirus infection through modulation of viral binding proteins on human bronchial epithelial cells[37]. For the management of acute bronchitis and acute respiratory tract infections (aRTI) in many countries in Europe, Asia, Australia, Central and South America, liquid herbal product preparations from the roots of *Pelargonium sidoides* have been licensed and marketed today. It interferes with reproduction of multiple respiratory viruses like the types of seasonal influenza A virus, human coronavirus, respiratory syncytial virus (RSV), coxsackie, and parainfluenza (Figure 1). Since respiratory viruses are expected to trigger > 90% of cases of acute antiviral bronchitis may lead to the beneficial effects of EPs® 7630 in patients with acute bronchitis[38,39].

Conclusions

As the global use of herbal medicinal products continues to expand and many newer products are introduced into the marketplace, there is also growing interest of the public in their uses. Several effective herbal therapies under evaluation in clinical trials for viral diseases to proof their effectiveness and safety. There is still much work to be done, however, to evaluate appropriate treatments, doses and formulations for these herbal preparations. Scientific work promoting modern drug discovery from phytochemicals will club conventional medicine practice. Scientific evidence on the comprehensive pharmacokinetic and pharmacodynamics of medicinal plants and their constituents should be made accessible to researchers and policy-makers in order to design and perform larger randomized multicenter clinical trials. The concept of integrating and introducing a specific herbal formulation as drug therapy can be turned into practice by taking these approaches.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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