Natural Products against Coronaviruses

Subjects: Infectious Diseases

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The SARS-CoV-2 belongs to the Coronaviridae family and the Coronavirinae subfamily which has been divided into four genera: α-coronavirus, β-coronavirus, γ-coronavirus and δ-coronavirus. The Human Coronavirus species HCoV (OC43, 229E, NL63 and HKU1), as well as those associated with Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and SARS-CoV-2, can cause respiratory tract infection but others such as the species 229E, OC43, HKU1, and NL63 usually cause the common cold.

Keywords: middle east respiratory syndrome (MERS) ; severe acute respiratory syndrome coronavirus (SARS-CoV) ; renin–angiotensin–aldosterone system (RAAS) ; angiotensin-converting enzyme inhibitors (ACEi) ; coronavirus disease of 2019 (COVID-19) ; medicinal plants ; antivi

1. Overview

COVID-19 is a pandemic disease caused by the SARS-CoV-2 virus, which is potentially fatal for vulnerable individuals. Disease management represents a challenge for many countries, given the shortage of medicines and hospital resources. The objective of this work was to review the medicinal plants, foods and natural products showing scientific evidence for host protection against various types of coronaviruses, with a focus on SARS-CoV-2. Natural products that mitigate the symptoms caused by various coronaviruses are also presented. Particular attention was placed on natural products that stabilize the Renin–Angiotensin–Aldosterone System (RAAS), which has been associated with the entry of the SARS-CoV-2 into human cells.

2. SARS-CoV-2

The Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was declared a pandemic on 11 March 2020 [1] and is probably the biggest challenge for public health systems in most countries given the limited knowledge about effective treatments [2].

The SARS-CoV-2 belongs to the Coronaviridae family and the Coronavirinae subfamily which has been divided into four genera: α-coronavirus, β-coronavirus, γ-coronavirus and δ-coronavirus [3]. The Human Coronavirus species HCoV (OC43, 229E, NL63 and HKU1), as well as those associated with Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and SARS-CoV-2, can cause respiratory tract infection but others such as the species 229E, OC43, HKU1, and NL63 usually cause the common cold [3]. Genetic characterization has shown that SARS-CoV-2 shares almost 80% of the SARS-CoV [4] and 96.2% of the bat β-coronaviruses lineage B [1] genomes. The SARS-CoV-2 belongs to the β-coronavirus group and causes milder symptoms than SARS and MERS but the transmission between people is much faster with an R0 (Basic Reproduction Number) of 3.28 [5] compared to the R0 values around 0.9 for MERS-CoV [2]. The mortality rate for SARS-CoV-2 is 3.4% compared to 9.6% and 35% for SARS-CoV and MERS respectively [6]. The incubation period for SARS is 2 to 10 days, while that of SARS-CoV-2 is 1 to 14 days (**Table 1**) [4]. Additionally, several studies reported that SARS-CoV-2 and SARS-CoV use the Angiotensin-Converting Enzyme 2 (ACE2) as a receptor to enter target cells, while MERS-CoV uses dipeptidyl peptidase 4 (DPP4) for the same purpose (**Table 1**) [2]. The alveolar lung and small intestine are potential targets for SARS-CoV-2 due to the high expression of ACE2 [1].

Table 1. Pathogenetic and epidemiological characteristics of SARS-CoV-2, SARS-CoV and MERS-CoV.

Species	Receptor	Incubation Period	RO	Case Fatality Rate	References
SARS-CoV-2	**ACE2**	**1 to 14 days**	**3.28**	**3.4**	**[3][5][7]**

Species	Receptor	Incubation Period	RO	Case Fatality Rate	References
SARS-CoV	ACE2	2 to 10 days	1.7–1.9	9.6	[4][8]
MERS-CoV	DPP4		0.9	35	[2]

SARS-CoV-2 mainly affects the middle-aged and elderly, as well as people with underlying diseases such as hypertension, diabetes, obesity or with heart and kidney problems, but shows low severity in children [7] although the disease transmission in this age group is still unknown [2] and the infection rates in children are increasing with the emergence of new SARS-CoV-2 variants [9].

Home isolation and quarantine have been applied in most countries to reduce the spread of the disease. However, this measure is also leading to economic, social and political deterioration in the affected countries. Consequently, the cases of anxiety and depression due to confinement as well as the number of deaths due to these causes have increased [10]. The enormous worldwide effort to develop vaccines against COVID-19 is recognized well-known as at least 19 vaccines have entered clinical trials and some vaccines already being applied to people in several countries [11]. However, the rushed development of a vaccine is usually accompanied by numerous challenges including potentially severe side effects and the possible loss of disease protection shortly after vaccination [12]. Moreover, the rise of new virus variants can affect the effectiveness of current treatments.

Similarly, other large-scale trials are in progress for the evaluation of possible therapies, including the World Health Organization (WHO) Solidarity Trial [11]. Pharmaceutical products undergoing clinical trials as potential treatments for COVID-19 include the antiviral nucleotide analog remdesivir, systemic interferons, and monoclonal antibodies [11]. Moreover, the antiparasitic drug ivermectin has been repurposed as a potential antiviral against SARS-CoV-2 and some drugs such as hydroxychloroquine that initially seemed promising have already been discarded by conflicting results through small-scale studies [12].

The accelerated search for a cure involves questions of a bioethical nature which prompts a reflection on the Declaration of Helsinki [2013] as well as the non-maleficence and beneficence principles to enable the use of untested procedures in clinical trials under emergency conditions [13]. It is necessary to implement a sustainable program to improve the health of citizens while a cure for SARS-CoV-2 is developed. Medicinal plants and natural products have the potential for enhancing people's health and boost the immune system [14]. Plants generally contain a combination of active ingredients or phytochemicals with different properties. Herbal medicinal formulations have been effective in treating emerging and reemerging viral diseases affecting diverse human and animal populations [14]. Plant extracts have shown specific antiviral properties in experimental animal models, which have prompted the formulation of natural products for the treatment of viral diseases [15]. Similarly, the bioactive compounds of medicinal plants can act as immunomodulators and can be combined with other therapies against viral diseases [16].

Natural products can help researchers design safe and easily accessible medical treatments [17]. For instance, plants from traditional Chinese medicine (TCM) such as *Scutellaria baicalensis* contain various antiviral compounds, including inhibitors of viral replication [18] and phytochemicals with anti-SARS-CoV-2 potential. Furthermore, 125 Chinese herbs were found to contain at least 2 of 13 compounds (betulinic acid, coumaroyltyramine, cryptotanshinone, desmethoxyreserpine, dihomo-γ-linolenic acid, dihydrotanshinone I, kaempferol, lignan, moupinamide, N-cis-feruloyltyramine, quercetin, sugiol, tanshinone IIa) that can inhibit the 3C-Like protease (3CLpro) and Papain-Like protease (PLpro) as well as block the entry, replication and binding of the SARS-CoV-2 Spike protein (S protein) [19]. Similarly, a protective effect against the 229E coronavirus was observed in respiratory cell cultures pre-treated with 50 µg/mL *Echinacea* [20]. In addition, the highly pathogenic SARS and MERS coronaviruses were also inactivated in vitro (IC_{50} 3.2 ug/mL) using the same plant. Other species such as grapefruit (*Citrus* × *paradisi*) have also been used to combat several respiratory infections [21].

The Renin–Angiotensin–Aldosterone System (RAAS) is a cascade of vasoactive peptides that regulate key processes in human physiology. SARS-CoV-1 and SARS-CoV-2 interfere with the RAAS by binding to the Angiotensin-Converting Enzyme 2 (ACE2) which serves as a receptor for both SARS viruses [22]. Overactivation of the RAAS by coronaviruses can contribute to the development of critical symptoms. Several common foods belonging to the families Alliaceae, Apiaceae, Brassicaceae, Cucurbitaceae, Rutaceae, Vitaceae, Zingiberaceae, among others have demonstrated the ability to regulate key RAAS processes [23][24].

Various countries such as Ecuador are considered megadiverse because of the high number of plant species. Various species from megadiverse areas have shown great potential for the treatment of respiratory conditions but have not been

tested against coronaviruses[22]. Further research is needed to assess the effect of these species against SARS-CoV-2. The pandemic impact of the 2002 SARS epidemic that began in Foshan, China [23][25], the high mortality rate and the subsequent re-emergence of the disease one year later [24] together with the economic problems caused in Asia encouraged research efforts focused on controlling coronaviruses infections by medicinal plants [26]. The aim of this review was to summarize the available literature on medicinal plants used against various types of coronaviruses, including SARS CoV-2 [25]. Special emphasis was placed on species located in Ecuador as one of the megadiverse countries.

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