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Review Article

Natural Products Derived from Plants and Seaweeds Against Clinical Importance Respiratory Viruses

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Abstract

Acute respiratory tract infections are the most common diseases in all individuals, regardless of age or sex. Epidemiological research and community-based studies conducted since the early 20th century have determined the rates of disease and the pathogens involved in such infections. More recently, advances in diagnostic techniques have enabled a more complete identification of the viruses involved in respiratory infections, which has aided in the ability to target specific therapeutic agents to the causative pathogens. Natural products have been used since earliest times as a treatment for various diseases. In this review, we show that natural products derived from plants and seaweed present promising results for several respiratory viruses such as human metapneumovirus (HPMV), Influenza, Respiratory Syncytial Virus (RSV), Rhinovirus, Paramyxovirus, Hantavirus, Adenovirus, Feline, Murine and other Human Coronaviruses, in addition to new therapeutic perspectives against COVID-19.

Keywords: Natural products; Plant; Algae; Antiviral; Respiratory; COVID-19

Introduction

Many viral species are of clinical importance and affect the world causing diseases in a large number of people. Among these, many studies mention different viruses such as Adenovirus [1], Coronavirus [2], Hantavirus [3], Orthomyxovirus [4], Paramyxovirus [5], Measles Virus [6], Rhinovirus [7] and the group that most affects people worldwide, Influenza Virus [8,9]. Natural products are widely used as alternative treatments for many diseases, whether viral, bacterial, parasitic or fungal. Many pathogens are resistant to synthetic and specific drugs for different targets. The study with natural products substances is important to increase the spectrum of treatment and reduce the incidence of microbial resistance to treatment acquired by pathogens with a smaller range of drugs [10].

Respiratory viruses have been a major public health problem since earlier times. Viral infections that directly affect the respiratory tract today include infections with the highest transmissible capacity and, such as Influenza, one of the highest mortality and morbidity rates worldwide [11]. Its characteristic of easy transmissibility occurs because the virus is found in droplets and secretions expelled by the respiratory system, justifying in most cases, the number of cases configured in pandemics [12,13]. Respiratory infections represent one of the highest case incidence rates among diseases that affect humans. The mortality rate of respiratory infections in developed countries is much lower than that of developing countries, precisely because of hygiene, sanitation and culture measures [14,15].

Respiratory viruses have a distribution based on seasonality, as they have a specific predominance in certain seasons. We can see Influenza and RSV infections especially in winter. Picornaviruses cause infections throughout the year, while Enteroviruses are more common in summer, and Rhinoviruses in winter [16]. Diseases that are caused by respiratory viruses can be classified as common colds, pharyngitis, laryngitis, acute bronchitis, pneumonia, among other complications commonly observed [17]. The immunosuppression factor can also cause openness to infections in the respiratory tract involving Cytomegalovirus, Echovirus, Coxsackie virus, that can cause severe conditions involving acute pharyngitis [18]. Globalization and ease of movement among people in different countries were factors that enabled the violent transmission of this respiratory virus. Today, we need government measures from Health authorities, the work of science and health professionals to control global infection [16].

Contingency plans are necessary to control the growth curve of these respiratory viruses. Contagion from infected droplets is concomitant with the overcrowding of public services, environments associated with urban transport. One of the most important measures to control the cases and growth of individuals infected with SARS-CoV-2 is social isolation. At-risk groups need to stay away from agglomerations precisely so that they are not exposed to infected patients [19].

Influenza

The influenza A, influenza B and influenza C viruses were isolated in 1933, 1940 and 1951 respectively. Both influenza A and B belong to the family Orthomyxoviridae and to the genus Influenzavirus [20]. Influenza C is in a specific genus since it is the only species of the genus, affecting humans and pigs. Influenza viruses are enveloped by a lipid bilayer containing their single-stranded negative sense RNA genome. The capsid of these viruses is of helical symmetry, with Influenza A and B composed of eight RNA segments and Influenza C by seven RNA segments. As for their characteristics of clinical importance, we can only categorize Influenza A and B, as they are significantly pathogenic to human hosts. Influenza C, on the other hand, causes a very rare infection and is usually associated with mild pathogenesis in the respiratory tract [9].

Adenovirus

The first isolation of adenovirus occurred from primary adenoid cell culture of children in the early 1950s. The icosahedral symmetry capsid that surrounds the linear stranded DNA genome of this enveloped virus has 12 vertices. Its infection is prevalent worldwide and the rate of infected people always varies between sporadic cases and epidemic periods. Adenoviruses have great stability in the environment, so they are easily transmitted indoors. Its clinical manifestation involves infections and diseases in the upper and lower respiratory tract, being considered a public health problem [1].

Respiratory Syncytial Virus (RSV)

Respiratory syncytial virus (RSV) was isolated in 1956 where an experimental chimpanzee displayed a disease similar to a common cold, demonstrating a human pathogen. RSV infection can cause severe manifestations in children at the lower respiratory tract. The most common afflictions are bronchiolitis and pneumonia. Patients with comorbidities and immunodeficiency have high risk factors for infection. These viruses belong to the Paramyxoviridae family and to the Pneumovirus genus, as well as they are single-stranded negative sense RNA viruses, not segmented, encoding about 10 viral proteins. Regular RSV epidemics follow seasonality, being common in winter and in temperate climates [9].

Rhinoviruses

Rhinoviruses have more than 100 serotypes and can cause respiratory diseases in the upper respiratory tract. These viruses are more common in children and are generally associated with many colds and febrile illnesses. Following the line of the other respiratory viruses, there are conditions in which the infection gets worse and becomes more serious. Patients with previous lung problems may experience pneumonia due to Rhinovirus infection. Rhinoviruses belong to the Picornaviridae family and usually grows at lower rates compared to other respiratory viruses [7].

Human Metapneumoviruses (hPMV)

HPMV or Human Metapneumovirus are responsible for approximately 2-12% of respiratory diseases in the pediatric lower respiratory tract. The virus is a member of the Paramyxoviridae family and the only one in the Metapneumovirus genus. Since its isolation in 2001, the biggest challenge for medicine and virology research is to understand the pathogenic mechanism of these viruses, precisely to develop effective antivirals and vaccines [21].

Hantaviruses

Hantaviruses are known to cause two distinct syndromes with hemorrhagic fever and hantavirus pulmonary syndrome (HPS). Consequently, Hantavirus infection should be considered one of the causes of respiratory diseases in areas where Hantaviruses are endemic. Hantaviruses are RNA viruses belonging to the Bunyaviridae family. Its most common reservoirs are rodents, moles, bats. And in contrast, the more these rodent carriers experience population imbalances, the greater the chances of an outbreak due to Hantavirus [3].

Measles Viruses

Measles viruses have an RNA genome, and they belong to the Morbilivirus genus and the Paramyxoviridae family. The Measles virus most often infects human hosts and non-human primates. Clinically, the Measles virus after the incubation period of 8-12 days can be observed with fever, cough, runny nose and in some cases, conjunctivitis. It can also be observed in patients as skin rashes, usually as erythematous spots on the face and neck. Measles viruses are capable of causing serious illness in children; however, we have a vaccine today for the major circulating strain [6].

Coronaviruses

Over the past 12 years, two novel β-CoVs, the severe acute respiratory syndrome CoV (SARS- CoV) and the Middle East respiratory syndrome CoV (MERS-CoV) have emerged, and these viruses can cause severe human diseases. The lack of effective drug treatment and the associated high morbidity and mortality rate of these two CoVs, as well as their potential to cause epidemics, highlight the need for novel drug discovery for the treatment of CoV infection [22]. In view of the current pandemic scenario for the new Coronavirus (SARS-CoV-2), the objective of this review is to show the therapeutic strategies involving natural products from plants and algae for respiratory viruses of clinical importance.

Coronaviruses have a wide diversity between hosts, in addition to a great variance in their cell tropism. The vast majority of alphacoronaviruses and beta coronaviruses infect mammals. At the same time, gamma and delta coronaviruses infect birds and some mammals [23]. By 2019, 6 different types of Coronaviruses capable of infecting humans have been reported: HCoV-229E; HCoV-OC43; HCoV-NL63 and HKU1 capable of inducing mild respiratory syndrome in humans. The most vulnerable hosts were babies and the elderly. Both SARS-CoV and MERS-CoV showed a more aggressive profile regarding infection, causing severe acute respiratory syndrome in human patients, presenting a mortality rate much higher than other Coronaviruses [24].

In January 2020, China concluded in laboratory tests that the unknown pathogen was a Coronavirus, confirmed by a test where the sample showed 95% homology with bat coronavirus and 70% similarity with SARS-CoV. As with all respiratory viruses, exponential growth was observed in a short time, even in people who had not had contact with the live animal market, immediately suggesting that community transmission was taking place [25]. SARS-CoV-2, characterized during the outbreak in China, that until 16/03/2020 was responsible for infecting more than 80,000 people (China) and more than 153,000 worldwide causes the disease now called COVID-19 [26].

All ages are susceptible to SARS-CoV-2 infection. Droplets, generated during coughing where this infected material is exposed to another individual's respiratory tract, are responsible for transmission. Asymptomatic people and those who have not yet manifested the symptoms are also able to transmit the virus. As much as all ages are susceptible to infection, there are individuals at a greater risk, such as elderly, patients living with HIV; Diabetics; Hypertensive and individuals who already had influenza infection [27] (Figure 1).

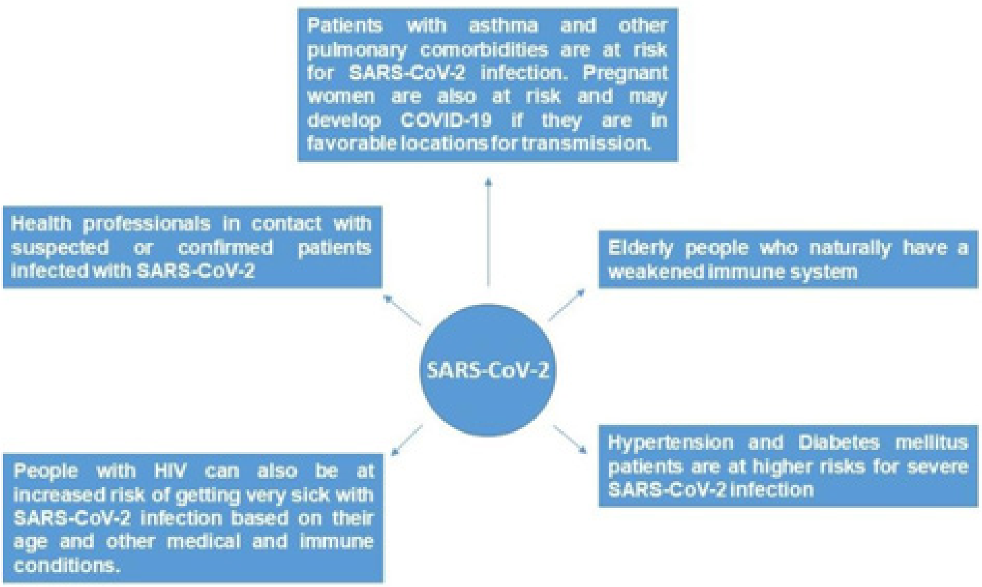

Figure 1: Scheme showing populations at risk for the new Coronavirus (SARS-CoV-2). HIV patients who have low CD4 counts or who are not being treated with antiretroviral are at risk. People with pulmonary comorbidities and respiratory diseases are more at risk of developing severe acute respiratory syndrome. Hypertensive and diabetes patients are also at risk. The elderly has a more fragile immune system, so they are at risk. Healthcare professionals should take all possible care when handling suspected or confirmed COVID-19 patients [28].

New perspectives involving treatment against respiratory viruses using natural products

Human coronavirus infections have been a public health problem since the 2002 SARS epidemic in China, where it affected thousands of patients. Viral respiratory diseases are responsible for a large number of deaths worldwide. With the absence of effective vaccines and effective antiviral therapies, natural products have been an excellent alternative against these pathogens [29,30]. Plant studies show many activities against respiratory viruses. The products produced by the most varied species of plants demonstrate potent antimicrobial inhibitory activities [31]. The products from plants can interact by inhibiting the neuraminidase present in the Influenza group viruses, a crucial enzyme in the replication process of these viruses in their target cell. The literature shows a series of activities derived from the products of these plants, such as the biflavonoids isolated from Ginkgo biloba and Glycyrrhiza uralensis that exhibits inhibitory activity against H1N1, being a potential inhibitor of neuraminidases (73). A list of studies done with plants that showed inhibitory activities of respiratory viruses is shown in table 1. Many Brazilian plants have medicinal activities and are already used by the population as medicines for several comorbidities [32]. Brazilian plants show different antiviral activities against different groups of pathogens such as HSV-1 (herpes simplex virus type 1), HSV-2 (herpes simplex virus type 2) and Poliovirus. Plants like Trixis praestans and Cunila spicata showed results against Adenovirus [33,34] (Table 1).

Table 1: List of studied species, target respiratory virus, results obtained and bibliographic references.

Plant species studied	Isolated Product or extract	Target respiratory virus	Results	References
Glycyrrhiza uralensis	Coumarines	Influenza A (H1N1)	Inhibition of viral NA*	[35]
Citrus junos	Flavonoids	Influenza A (H1N1)	EC_{50} = 918.5µg/ml	[36]
Scutellaria baicalensis	Flavonoids	Influenza A (H1N1)	Inhibition of viral sialidase	[9]
Polygonum punctatum	Aqueous extract	Respiratory syncytial virus (RSV)	EC_{50} = 120µg/ml	[45]
Lithraea molleoides	Aqueous extract	Respiratory syncytial virus (RSV)	EC_{50} = 78µg/ml	[45]
Myrcianthes cisplatensis	Aqueous extract	Respiratory syncytial virus (RSV)	EC_{50} = 87µg/ml	[45]
Amelanchier alnifolia	Methanolic extract	Coronavirus (SARS-CoV)	Inhibition > 90%	[67]
Rosa nutkana	Methanolic extract	Coronavirus (SARS-Cov)	Inhibition > 90%	[67]
Sambucus racemose	Methanolic extract	Respiratory syncytial virus (RSV)	Inhibition > 90%	[67]
Hypericum perforatum	Isoquercetin	Influenza A	EC_{50} = 1.2µg/mL	[42]
Elsholtzia rugulosa	Crude Extract	Influenza A (H1N1/H3N2)	EC_{50}= 122.60/123.84µg/Ml	[58]
Geranium sanguineum L	Extract	Influenza	Reduction of Infectivity in vitro	[73]
Elderberry	Extract	Influenza	Efficient and support	[73]
Guazuma ulmifolia	Extract	Poliovirus	Inhibited poliovirus replication	[73]
Lycoris radiate (Lycorin)	Isolated product	Coronavirus (SARS-CoV)	Anti-SARS-CoV activity	[73]
Black soybean	Extract	Human Adenovirus type 1	Inhibition in a dose- dependent	[73]
Stryphnodendron adstringens	Extract	Poliovirus	Inhibited poliovirus replication	[73]
Isatis indigotica	Extract	Coronavirus (SARS-CoV)	EC_{50} = 191.6µg/ml	[57]
Chamaecyparis obtusa	Extract	Coronavirus (SARS-CoV)	In vitro activity against SARS-CoV	[111]
Hippeastrum hybrid	Lectin	Coronavirus (SARS-CoV)	EC_{50}=3.2±2.8µg/ml	[39]
Galanthus nivalis	Lectin	Coronavirus (SARS-CoV)	EC_{50}=6.2±0.6µg/ml	[39]
Narcissus pseudonarcissus	Lectin	Coronavirus (SARS-CoV)	EC_{50}=5.7±4.4µg/ml	[39]
Allium porrum	Lectin	Coronavirus (SARS-CoV)	EC50 = 0.45 ± 0.08 µg/ml	[39]
Allium ursinum	Lectin	Coronavirus (SARS-CoV)	EC_{50} = 18 ± 4µg/ml	[39]
Morus Nigra	Lectin	Coronavirus (SARS-CoV)	EC50=50±13µg/ml	[39]
Tulipa hybrid	Lectin	Coronavirus (SARS-CoV)	EC_{50} = 22 ± 6µg/ml	[39]
Cymbidium hybrid	Lectin	Coronavirus (SARS-CoV)	EC_{50}=4.9±0.8µg/ml	[39]
Polygonatum multiflorum tetramer	Lectin	Coronavirus (SARS-CoV)	EC_{50}=18 ± 13µg/ml	[39]
Sophorae radix	Extract	MHV (CoV - in vivo prototype)	EC_{50} = 0.8µg/ml	[41]

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Acanthopanacis cortex	Extract	MHV (CoV - in vivo prototype)	EC_{50} = 0.9µg/ml	[41]
Sanguisorbae radix	Extract	MHV (CoV - in vivo prototype)	EC_{50} = 3.7µg/ml	[41]
Scrophularia scorodonia	Isolated Product	Human Coronavirus (HCoV -229E)	EC_{50} = 1.7µmol/L	[15]

EC_{50} Concentration of the substance capable of inhibiting the virus by 50%; *NA -Neuraminidase; MHV -Mouse hepatitis virus

Research on natural products has already shown activity of plants inhibiting the replication of Coronaviruses, which are viruses of clinical importance for human health [37]. Native plants from Asia, already used by oriental medicine, tested for HSV-1 and HIV-1, were tested against SARS-CoV, and obtained promising results as protease inhibitors, interfering in the replicative cycle of these viruses [38,39]. The natural products isolated from marine organisms have many described activities. Algae can have antibacterial, antimalarial, antifungal, antiparasitic and antiviral activities. Many studies obtained by various groups against viruses in general (HSV-1, HIV-1, ZIKV and CHIKV) the antiviral activity of red, green and brown algae. Whether from their extracts or from isolated products, for example Caulerpin, which is an isolate from the green alga Caulerpa racemosa [40-45].

Researches on antiviral activity of algae products against respiratory viruses show activity of green algae such as Ulva fasciata (table 2) acting on the replication of Human Metapneumovirus (HMPV) [21]. Blue green Cyanophyta algae activity against Paramyxovirus is also observed [46]. The natural products from algae are also able to act against the replication of viruses such as Echovirus, Rhinovirus, Adenovirus and Vaccinia virus [47,48]. The extracts of the algae Constantinea simplex and Farlowia mollis demonstrate potent activities against the Vaccinia virus, that causes serious infections in the respiratory tract of both humans and animal hosts [49,50] (Table 2).

Table 2: List of studied species, target respiratory virus, results obtained and bibliographic references.

Algae species studied	Isolated Product or extract	Target respiratory virus	Results	References
Aphanocapsa elachista	Aqueous extract	RSV	EC_{50} = 1.25µg/ml	[57]
Nostoe sphaericum	CH_2Cl_2 extract	RSV	EC_{50} = 5µg/ml	[57]
Anabaena doliolum	Aqueous extract	RSV	EC_{50} = <10µg/ml	[57]
Synechococcus elongatus	Aqueous extract	RSV	EC_{50} = 100µg/ml	[57]
Phormidium foveolarum	CH_2Cl_2 extract	RSV	EC_{50} = 271µg/ml	[57]
Ulva fasciata	Crude extract	HMPV	Inhibition of viral replication	[58]
Kappaphycus alvarezii	Lectin	Influenza	EC_{50} = 1.7nM	[79]
Sargassum hemiphyllum	Methanolic extract	Influenza	Inhibition of viral replication	[63]
Constantinea simplex	Aqueous extract	Coxsackie B5	Viral titer reduction	[21, 72]
Ecklonia cava	Isolated Product	SARS-CoV	EC_{50} = 2.7µM	[65]
Turbinaria conoides	Isolated Product	Feline Coronavirus	EC_{50} = >100 µg mL	[41]
Turbinaria ornata	Ethanolic extract	NDV (New Castle Virus)	Inhibition of viral replication	[32]
Griffithsia sp.	Lectin	MERS-CoV	Inhibition of adsorption	[60]
Porphyridium sp.	Sulfated polysaccharides	SARS-CoV-2	Inhibition of adsorption	[62]

EC_{50} Concentration of the substance capable of inhibiting the virus by 50%; RSV-Respiratory Syncytial Virus; HMPV-Human Metapneumovirus

Marine natural products also show inhibitory activity against human Coronaviruses. Tests with extracts of red algae such as those of the Rhodophyceae genus showed anti-SARS-CoV and anti-Influenza activities [51]. Betting on the wide spectrum of inhibitory activities of marine products, in silico studies are also carried out to look for promising combinations of potential SARS-CoV inhibitors [52]. The sulfated polysaccharides of the Porphyridium sp. are shown to inhibit Coronavirus replication and the study by Mahadev et al; showed that the products from this algae have great biocompatibility with products used in hygiene and prophylaxis against Coronaviruses, including SARS-CoV-2, which causes COVID-19 [53].

Conclusion

Respiratory viruses are responsible for thousands of deaths of people every year and their pathogens infect children, adults and the elderly, making it a major public health problem. Although we have a flu vaccine, we still need more research and development of prophylactic alternatives and specific antiviral treatments for many diseases that end up creating chaotic situations around the world. Many studies are needed to develop and approve a reference drug in treatment for these diseases. In vitro and in vivo studies need to be carried out to ensure the safety and proven efficacy of the drug so that it is directed to humans in the clinical phase. The same process is categorized in vaccines, and this takes time and study.

Natural products from plants and algae are a very effective alternative in studies aimed at the development of new antiviral drugs. Studies involving the mechanism of action of these drugs against respiratory viruses and the question of the bioavailability of these products for large-scale production are very important issues for the future of antivirals derived from natural products.

Compliance with Ethical Standards

This article does not contain any studies with human participants performed by any of the authors.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this article.

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