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Plant lectins have antagonistic effects against Coronavirus family: Natural products can control Coronaviral infections: A review

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Abstract From the end of December 2019, Corona Virus Disease – 19 (COVID – 19) is the fear of people throughout the world. The causal organism behind COVID – 19 is SARS – CoV – 2 (Severe acute respiratory syndrome corona virus). This virus creates respiratory problems in human beings. WHO declared COVID – 19 as a pandemic disease because of its severe infection development capability. Like many other enveloped viruses, SARS – CoV – 2 carries glycoproteins on their surface. These glycoproteins are mainly responsible for the infection processes. They have involved in the receptor binding phenomenon. These glycoproteins are also involved in retrovirus particle and host cell membrane fusion. So, they may be potential targets for the development of novel corona viral therapies. Carbohydrate - Binding Agents (commonly called CBA) have antiviral activity towards the Corona virus. Plant lectins have anti-viral activities against Coronavirus species. In this review, we discussed thoroughly about the role of plant lectins in destroying Coronavirus infection. Plant lectins may be the potential source of herbal drugs of COVID – 19.

Keywords: COVID – 19, Pandemic, SARS – CoV, Lectin, Algae, Herbal drug

Introduction

Coronavirus disease (COVID – 19) is a highly infectious disease that causes mild to severe respiratory troubles. Older people (more than 60 years) and those people who lack a strong immunity system are prone to get this viral infection. People having cardiovascular disease, diabetes, chronic respiratory disease are more likely to get COVID – 19 infections. As per WHO reports, COVID -19 can affect different people in different aspects. Common symptoms of this disease are; fever, tiredness, high cough. Few other symptoms are like, shortness of breath, aches and pains, sore throat, running nose, nausea, and diarrhea **(**WHO REPORT MARCH 11,2020). Mainly this virus creates

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pneumonia in human beings. This is a fatal disease by causing death to people. According to symptoms, COVID -19 is renamed as severe acute respiratory syndrome coronavirus (SARS-CoV) by the members of the International Committee on Taxonomy of Viruses (ICTV) (Majumdar *et al.,* 2020). COVID 19 is considered as the global pandemic by crossing continental barriers.

The pandemic began in Wuhan city of China. It was first reported on December 31st, 2019 in Wuhan city of China (Majumdar *et al.,* 2020). Then it spread the rest of the world including Asia, Europe, and America. This disease is affecting 1696588 numbers of individuals and has caused 105952 deaths till 12th April as per WHO reports (WHO REPORT MARCH 16, 2020). The virus has a bat as its primary reservoir. It is speculated, the spread of the Coronavirus happened by eating bush meat that caused the crossing of the species barrier. In this review, we discuss thoroughly the antiviral activities of carbohydrate - binding plant lectins. Plant lectins have the potentiality in controlling RNA viral infections. It has a positive role in destroying the Coronavirus too (Meer *et al.,*2007).

Coronavirus genomic diversity is highly available in china: Wuhan is the epicenter of Coronavirus: epidemiological aspects

China is the most populous nation in the world. Most of the Coronavirus species were named by Chinese scientists studying local bats. For that reason, China is a likely hotspot of this viral disease (Fan *et al.,* 2019). A novel beta Coronavirus named novel Coronavirus 2019 (2019-nCoV), has recently developed a huge of pneumonia disease in Wuhan city of Hubei state, China. The Coronavirus infected person (COVID 19) was first reported in November 2019 in Wuhan province of China. By 2nd January 2020, 41 patients admitted in hospitals with confirmed cases of 2019-nCoV infection. 49% of the 2019-nCoV-infected patients were aged between 25–49 years, and 34% were aged between 50–64 years.

The median age of the patients was 49 years. Of the 41 patients, 32% were admitted to the Intensive Care Unit (ICU) because they required high-flow nasal cannula or higher-level oxygen support measures to correct the hypoxemia. Most of the infected patients were men 73% approximately. The number of deaths increased quickly after a few days of viral infection. As of Jan 24, 2020, 835 confirmed 2019-nCoV infections were reported in China, with 25 deaths. Reports have been released of the spread of cases in many provinces in

China, and other countries. Near about 3331 individual's death happened in China in Corona viral infection as of now.

Coronavirus infection is a pandemic disease

Coronavirus is not only crossed the species barrier but also crossed the continental barrier. During the past three weeks, Coronavirus disease 2019 (COVID-19) is rapidly expanding in all continents especially in Europe, North America, Asia, and, the Middle East. By March 16, 2020, the number of cases of COVID-19 outside China increased drastically and the number of affected countries, states and territories reporting infections to the World Health Organization (WHO) were143. Based on "alarming levels of spread and severity, and by the alarming levels of inaction", on March 11, 2020, the Director-General of WHO declared COVID-19 as pandemic WHO REPORT MARCH 16, 2020). As of today, the death rate is highest in the USA, followed by Italy and Spain. The countries having more than 10,000 confirmed cases are United States, Spain, Italy, Germany, China, France, Iran, UK, Turkey, Belgium, Switzerland, Netherlands, Canada, Brazil, Portugal, Austria and, South Korea. This vast spread of COVID – 19 diseases shows its pandemic nature (Figure 1).

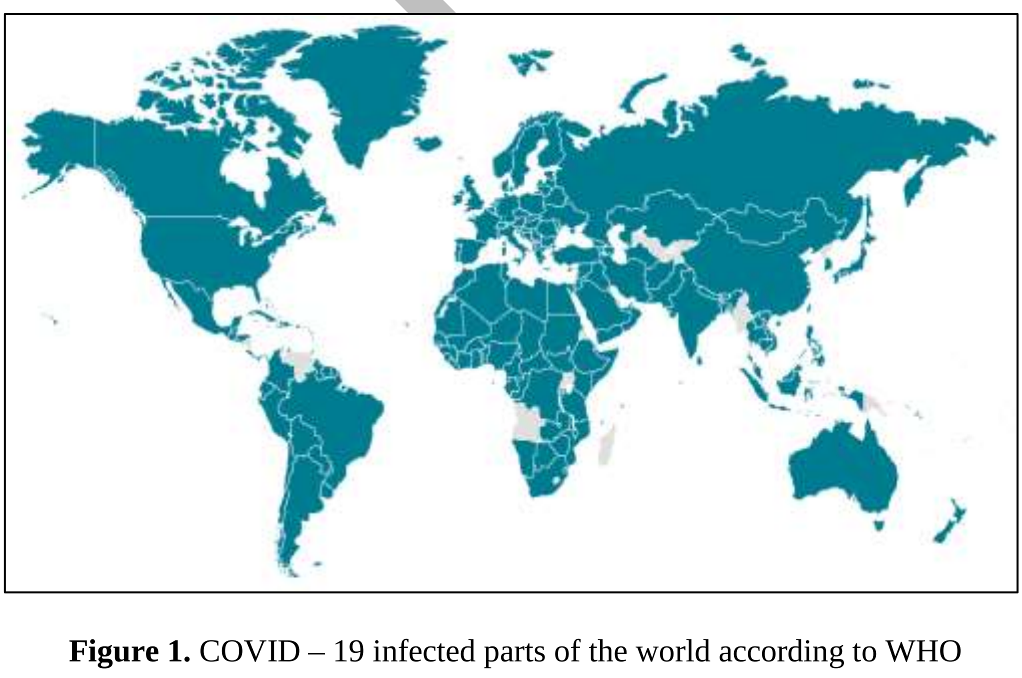

Figure 1. COVID – 19 infected parts of the world according to WHO

Did the Coronavirus cross - species barrier?

Bats are the only genus of mammals with the ability of flight. So, the migration rate is higher in bats among all mammals. They are distributed worldwide. It is postulated that flight generated the natural selection pressure for the coexistence of bats with viruses. The ability of migration of bats has the relevant potentiality of disease transmission (Wang and Cowled, 2015).

Bats are linked to several types of Corona viral pathogenic human diseases, supporting this hypothesis. CoVs like SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus), MERS-CoV(Middle East Respiratory Syndrome Coronavirus) and SADS-CoV (Swine Acute Diarrhea Syndrome Coronavirus), which is a great threat to human health (Wang and Cowled, 2015, Yang *et al.,* 2019). Bats are now recognized as important reservoir hosts of CoVs. Bats are the storage of viruses of MERS-CoV. Camels can also transmit this viral infection to humans directly (Zaki *et al.*, 2012). The most recent SADS-CoV fatal infection was traced back to bats (Zhou *et al.*, 2018).

Coronavirus taxonomy and structure

Coronaviruses (CoVs) belong to the subfamily Orthocoronavirinae in the family Coronaviridae and the order Nidovirales. CoVs are enveloped, crown-like viral particles. The genome structure is a positive-sense, single-strand RNA (+ssRNA), of 27–32 kb in size. It is the second largest of all RNA virus genomes. The genome also encodes for four structural proteins spike, envelope, membrane, nucleo capsid and, other accessory proteins. The length of the genome is dependent on the number and size of accessory proteins (Coronavirinae, 2019). Corona virus family comprised of alpha, beta, gamma and, delta Coronaviruses. Under the electron microscope, the spherical crown - shaped structure is distinctly observed by the scientists. For having the crown - like structure, the family is named as Coronavirus family **(**Kim *et al.,* 2020).

The expanded genome size of CoVs is believed to be associated with increased replication fidelity compared to other RNA viruses (Subissi *et al.*, 2014).

For that reason, genome changes caused by recombination, gene interchange, and gene insertion or deletion are common among all Coronavirus species. The number of species will continue to increase, as there are still many unclassified CoVs **(**Ge *et al.*,2016, Wu *et al.*, 2016). Two highly pathogenic

CoVs, SARS-CoV, and MERS-CoV have caused pandemic diseases in humans since 2002 (Drosten *et al.*, 2003, Zaki *et al.*, 2012). Mainly six types of Coronavirus species are fatal to the human beings. These are Coronavirus 229E, OC43, NL63, and HKU1, SARS – CoV and, MERS-CoV. Originating in China and then spreading to other parts of the world, SARS-CoV infected around 8000 individuals with an overall mortality of 10% during the 2002–2003 pandemic (Graham *et al.*, 2013). In 2012 in the Middle East, MERS-CoV spread to 27 countries. Besides these two viruses, CoVs 229E and NL63 and CoVs OC43 and HKU1 can also cause respiratory diseases in human beings (Kumaki *et al.*, 2011) as seen in Table1.

Table 1. Several human Coronavirus species

Coronavirus species	**Coronavirus genus**	**Present in china**	**Effective as a human pathogen**
Human Coronavirus 229E	Alphacoronavirus	Yes	Yes
Severe acute respiratory syndrome-related Coronavirus	Betacoronavirus	Yes	Yes
Middle East respiratory syndrome-related Coronavirus	Betacoronavirus	Yes	Yes
Rhinolophus bat Coronavirus HKU2 (SADS)	Alphacoronavirus	Yes	Yes
Murine Coronavirus (Murine hepatitis Coronavirus)	Betacoronavirus	Yes	Yes
Human Coronavirus HKU1	Alphacoronavirus	Yes	Yes
Betacoronavirus 1 (Human Coronavirus OC43)	Betacoronavirus	Yes	Yes

Plant lectins can stop viral propagation

Till today a huge number of lectins are identified from several natural sources like plants and fungi. These proteins have several structural scaffolds. Along with that these proteins have specific sites for mannose containing glycans. These mannose - binding carbohydrate pockets are very small in structure. These pockets have several sites responsible for broad sugar - binding specificity. Plant lectins are glycoprotein groups with the capability of recognizing and binding to sugar specific residues. Plant lectins are the major part of the plant defense system. They are the component of plant innate immunity (Lannoo and Damme, 2014). MBL i.e. mannose - binding lectins ultimately follow the lectin pathway of complement systems. Finally, they enter MAC (Membrane Attack Complex) and create perforations in the viral body. Most lectins are found in the seeds of the Leguminaceae family. Other than that, lectins were isolated and collected from leaves, fruits, tubers, root, rhizomes, and barks of several plants. Lectins have antiviral property and can help in controlling viral propagation. Lectins have an antagonistic effect against single stranded RNA viruses. It has antagonistic effect on several single -stranded RNA viruses. It is potentially effective against human immunodeficiency virus (HIV) as well as the Coronavirus (Shibuya *et al.*, 1986).

Lectins found in higher plants

Urtica dioica (common name: Stinging nettle) accumulates a low molecular weight lectin named *Urtica dioica* Agglutinin (UDA). UDA is a single polypeptide chain and very stable. Wheat Gram Agglutinin (WGA) derived from wheat similar to *Urtica dioica* Agglutinin UDA. These kinds of lectins are found in *Datura stramonium* seeds and potato plants.
Hippeastrum hybrid, *Galanthus nivalis* plants produces lectins that can destroy Coronavirus. Apart from that, *Cymbidium hybrid* from Orchidaceae family has lectins with anti-Corona viral property (Balzarini *et al.*, 1992; Mazalovska *et al.*, 2018; Singh and Walia, 2018).

Lectins found from marine algae can stop Coronavirus growth

Around 800 marine algae produce antiviral lectins. Amongst red marine algae, a lectin from *Griffithsia* sp. (GRFT) has been widely studied (Millet *et al.* 2016). GRFT has the potentiality of antagonistic effects on retroviruses (Shibuya *et al.*, 1986).

Plant lectins target glycans of Coronavirus envelope glycoproteins

Plant lectins are one kind of plant protein that has an antagonistic effect on RNA – viruses i.e. retroviruses. Coronavirus is susceptible to plant lectins. Many RNA viruses have carbohydrates - containing proteins i.e. glycol proteins in their surface. These glycoproteins are involved in the fusion of viral coats and membranes. CBA (Carbohydrate binding agents) target the two glycosylated envelope glycoproteins. These glycoproteins are the spike (S) and membrane (M) proteins, of several retroviruses. It did not inhibit the virus coat and cell membrane attachment. Rather, it affected virus entry at a post-binding stage. The sensitivity of Coronaviruses towards CBA is dependent on the mechanisms of the N-linked carbohydrates. Inhibition of mannosidases in host cells rendered the progeny viruses more sensitive to the mannose-binding lectins. It is sensitive to N-acetylglucosamine binding UDA. These results show that CBA exhibits promising capabilities to inhibit Coronavirus infections.

GRFT also prevents SARS Coronavirus (SARS-CoV) infection *in vitro* and *in vivo*, through specific binding to its spike glycoprotein. It shows activity against multiple other Coronaviruses pathogenic to humans, other mammals, and birds. The Middle East respiratory syndrome coronavirus (Marco), another highly pathogenic human Coronavirus, is inhibited at the entry - level by GRFT to prevent infection *in vitro* (Mori, 2005).

Also, *Hippeastrum hybrid* agglutinin (HHA), *Galanthus nivalis* agglutinin (GNA), *Cymbidium* agglutinin (CA), and *Urtica dioica* agglutinin (UDA) demonstrate antiviral activities against Coronaviruses *in vitro* also in i*n vivo* (Keyaerts *et al.,* 2007). In an impressive screening of several plant lectins, remarkable antiviral effects on SARS-CoV observed by (Keyaerts *et al.,* 2007) with EC50 values i.e. effective concentration 50 percent (%) at low microgram/ mililitre (μg/ml) levels were observed, with strongest activities found predominantly among mannose binding lectins. Based on these data, lectins should be included in antiviral strategies to fight SARS Coronavirus infections. Moreover, Tobacco lectins are also involved in anti-corona viral activities (Table 2 and Figures. 2-5).

Table 2. Several types of lectins, source plants and their effective concentration against SARS-Cov

Antiviral lectins	Collected from	Common name	Type	Family	Ec50
***Hippeastrum hybrid* agglutinin (HHA)**	*Hippeastrum hybrid*	Amaryllis	Monocot	Amaryllidaceae	3.2 μg/ml
***Galanthus nivalis* (GNA)**	*Galanthus nivalis*	Snowdrop	Monocot	Amaryllidaceae	6.2 μg/ml
***Cymbidium hybrid* agglutinin (CA)**	*Cymbidium hybrid*	Cymbidium orchid	Monocot	Orchidaceae	4.9 μg/ml
***Urtica dioica* agglutinin (UDA)**	*Urtica dioica*	Stinging nettle	Dicot	Urticaceae	1.3 μM

Sources: Balzarini *et al.* (1992), Keyaerts *et al.* (2007), Mazalovska and Kouokam (2018), Singh and Walia (2018)

Figure 2.*Cymbidium hybrid* Plant

Figure 3.*Galanthus nivalis* Plant

Figure 4.*Hippeastrum hybrid* Plant

Figure 5.*Urtica dioica* Plant

Conclusion and future strategies

In this review, we discussed spread of the Coronavirus from Wuhan, China, the destructive nature of this pandemic disease. We focused on several plant - derived lectins and their anti-corona viral activities. These plant lectins may be the potential source of herbal drugs against Coronavirus. The exact transmission route of COVID – 19 in the human body is still under research. Exact drugs to control this pandemic are still under research. During a productive Coronavirus infection, the Spike protein undergoes a series of conformational changes following the attachment to the viral receptor molecule. This interaction eventually develops the fusion of the viral envelope with the host cell membrane. CBA is likely to interfere during the virus entry process by attaching to the N-glycans of the Spike protein.

For the SARS Coronavirus, CBA was proposed to exhibit a dual mode of action: inhibiting both virus fusion and exocytosis or viral egress from the cell. CBA interfere with the Coronavirus entry process by targeting of the N-glycosylated Membrane and Spike proteins. Furthermore, the antiviral efficiency of the CBA was significantly affected by the maturation of the N-glycans on the envelope glycoproteins. This disease creates socio - economic imbalance apart from serious health problems. After taking several safety mechanisms like washing hands, use of sanitizers, lockdown, and social isolation this pandemic killed more than one lakh people all over the world. Mannose specific plant lectins are the potential therapeutic agents for mitigating this disease. These plant lectins may develop potential cheap herbal drugs which may cause fewer side effects and help human society.

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