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Possible role of traditional medicinal plant Neem (*Azadirachta indica*) for the management of COVID-19 infection

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ABSTRACT



The novel corona virus disease (COVID-19) was originated from Wuhan, China. Afterwards, COVID-19 outbreak was declared as a Public Health Emergency of International Concern by the World Health Organization (WHO). Now, around two and a half million people are suffering and several thousand are dead worldwide due to the highly infectious and deadly nature of the virus. Unfortunately, no standard medicine or vaccine is available to treat the disease. The major clinical symptoms of COVID-19 are fever, chills, cough, fatigue, respiratory symptoms, diarrhoea, and shortness of breath. Clinical symptom-based Indian traditional medicinal practices like Ayurveda and Siddha could be beneficial to treat and prevent the infection. Indian origin traditional medicinal plant Neem (*Azadirachta indica*) has been reported to have antiviral potential against bovine herpes virus type-1, poliovirus type 1, duck plague virus, dengue virus type-2, newcastle disease virus, infectious bursal disease virus, avian influenza virus, and group B coxsackievirus. Neem is widely used as Ayurvedic medicine to treat fever, cough, asthma, and diarrhoea, which are also reported as the common clinical symptoms of COVID-19. Neem is reported to enhance both humoral and cell-mediated immune response during viral infection. Multidimensional antiviral therapeutic potentials of Neem insist on hypothesizing its probable application to control COVID-19 along with modern medicinal practices. But, a series of experimental database and translational research is required to establish the hypothesis.

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INTRODUCTION

COVID-19 outbreak

The World Health Organization (WHO) declared novel corona virus disease (COVID-19) outbreak as a Public Health Emergency of International Concern on January 30, 2020. Earlier, COVID-19 was also known as 2019-nCoV. It originated from Wuhan city of Hubei province in China (Xiang *et al.*, 2020). On March 11, 2020, the WHO declared COVID-19 outbreak as a pandemic (Cucinotta and Vanelli, 2020). According to the WHO, as of April 22, 2020 (05:30 GMT+5:30), about 24,71,136 people were suffering and over 1,69,006 had died due to corona virus infection from 213 countries worldwide. Corona virus infection might result in massive alveolar damage and progressive respiratory failure. The initial clinical symptoms are fever, chills, cough, fatigue,

respiratory symptoms, diarrhoea, and shortness of breath (Xu *et al.*, 2020; Chan *et al.*, 2020). Standard vaccines and antiviral agents could be beneficial to prevent and treat this disease. Unfortunately, there is no such medicine identified yet to treat COVID-19. Development of antiviral drug or vaccine may require months or years when immediate treatment is required to stop this highly infectious disease. The Chinese government is appreciating the use of traditional herbal medicine for the treatment of COVID-19 patients (hai Zhang *et al.*, 2020). Traditional Chinese medicine was found to be beneficial and effective to treat severe acute respiratory syndrome associated coronavirus (SARS-CoV) infection (Li *et al.*, 2005; Wen *et al.*, 2011). However, herbal treatments are mainly dependent on the sign and symptoms of the patients. Further studies are required to specifically target viral causes (hai Zhang *et al.*, 2020). In this sense, traditional herbal plants having antiviral potential can be used to treat COVID-19 infection depending upon sign and symptoms.

Neem (*Azadirachta indica*) as an antiviral agent

Indian origin traditional medicinal plant Neem (*Azadirachta indica*) has been used to treat several acute and chronic diseases in different parts of Asia and Africa from the ancient period. The medicinal importance of Neem has been mentioned in the Indian, age-old medical systems like Ayurveda and Siddha. The insecticidal, antimicrobial, larvicidal, antimalarial, antibacterial, antiviral, and spermicidal effect of different parts of the plant, including flowers, leaves, seeds and barks, was found to be beneficial to treat several microbial diseases (Gupta *et al.*, 2017). Neem has been denoted as "the tree of the 21st century" by the United Nations for its multi-therapeutic application (Tapanelli *et al.*, 2016). Water extracted polysaccharides (pectic arabinogalactan) from *Azadirachta indica* leaves was found to have antiviral activity against bovine herpes virus type-1 (BoHV-1) (Kumar and Navaratnam, 2013). *Azadirachta indica* leaves derived polysaccharides were also observed to have in vitro antiviral potential against poliovirus type 1 (PV-1) (Faccin-Galhardi *et al.*, 2012). Neem seed kernel extract was observed to have in vitro antiviral effect against duck plague virus (Xu *et al.*, 2012). Neem bark extract was found to be effective against herpes simplex virus type-1 under in vitro condition (Tiwari *et al.*, 2009). Neem oil was found to have in vitro antiviral effect against polio (SaiRam *et al.*, 2000). Aqueous extract of Neem leaves was found to have both in vivo and in vitro antiviral potential against dengue virus type-2 (Parida *et al.*, 2002). Neem leaves in broiler feed were recorded to be beneficial for immunity of commercial broilers

against Newcastle disease and infectious bursal disease like viral infections (Zahid *et al.*, 2013). Neem bark extract and leaf extract were found to have antiviral potential against highly pathogenic avian influenza virus (H5N1) (Schoonheim-Klein *et al.*, 2016) and group B coxsackieviruses (Badam *et al.*, 1999), respectively.

Possible application of Neem for COVID-19 treatment

Fever, cough, respiratory symptoms, and shortness of breath are reported as the common clinical symptoms for COVID-19 infected patients (Xu *et al.*, 2020). Neem leaf crude extract is a widely used Ayurvedic medicine to treat normal fever and malarial fever (Al-Hashemi and Hossain, 2016; Sujarwo *et al.*, 2016). Crude aqueous extract of Neem leaves was also recorded to be effective against Dengue fever-related clinical symptoms in suckling mice model. The Neem leaves extract was observed to have inhibitory potential on Dengue virus type-2 replication under both in vivo and in vitro conditions (Parida *et al.*, 2002). Neem twig had been mentioned in Ayurveda to relieve cough and asthma (Biswas *et al.*, 2002). Diarrhoea is another commonly observed clinical symptom for COVID-19 infected patients. Neem leaves are used to treat gastrointestinal disorder like diarrhoea in different parts of India as a traditional practice (Thakurta *et al.*, 2007). Additionally, Neem leaf, flower, and stem bark extracts were observed to have strong antioxidant potential (Sithisarn *et al.*, 2005). The extract of dried Neem leaves was recorded to enhance antioxidants in the rat model (Ghatule *et al.*, 2012). Neem bark extract was observed to have antioxidant potential by directly scavenging the hydroxyl radical (OH) and preventing the hydroxyl radical-mediated oxidative damage in the rat model (Bandyopadhyay *et al.*, 2002). Most importantly, Neem leaves extract was reported to induce a cell-mediated and humoral immune response in albino mice model (Ray *et al.*, 1996). Neem leaf glycoprotein was observed to be effective in maintaining normal immune homeostasis by upregulating type 1 response in mice (Bose *et al.*, 2009). Aqueous preparation of Neem leaf was also observed to enhance Th1 type immune responses against breast tumour associated antigen in mice and rat (Mandal-Ghosh *et al.*, 2007). Studies suggested that Neem leaves in broiler feed could be beneficial for the antibody production against the new-castle and infectious bursal disease viruses (Zahid *et al.*, 2013). Similarly, Neem leaf extract was found to enhance immunity in HIV/AIDS patients by increases CD4⁺ cell levels (Mbah *et al.*, 2007). Even Neem leaf extract was reported to act as an adjuvant

to increase the immunogenicity of poorly immunogenic surface antigen vaccine in mice model (Baral *et al.*, 2005). Neem leaf glycoprotein was observed to induce dendritic cell maturation (Goswami *et al.*, 2010) and macrophage-mediated antigen presentation in mice model (Sarkar *et al.*, 2008).

No experimental data is available to correlate the medicinal potential of Neem for the treatment of COVID-19 patients. Due to its multidimensional therapeutic potential, it can be hypothesized that Neem could be an effective ayurvedic medicine for the prevention and treatment of COVID-19 in addition to modern medicinal practices. A series of experimental database and translational research is required to establish the standard formulation of Neem or Neem-derived components to treat or prevent highly infectious COVID-19.

CONCLUSIONS

Neem is a widely used ayurvedic medicine having antiviral potential. Neem could be a probable ayurvedic medicine to prevent and treat COVID-19 infection through enhancement of immune response. Strong antioxidant potential of Neem may play a beneficial role during the treatment of highly infectious and deadly viral disease.

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Conflict of Interest

The authors do not have any conflict of interest associated with this publication.

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