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A review on SARS-CoV-2 and medicinal plants of Northeast India: their potential against COVID-19

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Abstract

Covid-19, the worst humanitarian crisis in the form of zoonotic pandemic has covered the entire globe over 210 countries and is continuing to spread around the world. It has crushed the entire world's health care system while illuminating the gaps in multiple fronts. Currently, Supportive treatment is offered with synthetic modern medicines and preventive measures including vaccines and personal hygiene. From decades, ethnobotanical studies and research have elucidated the use of medicinal plants and plant based products in combating against viral diseases. Highly potential bioactive compounds from plants with pharmacological properties can perform with minimal toxicity as compared to synthetic medicines with adverse effects. Ethnobotanical studies related to plants have blessed mankind during earlier pandemics. This review explains the possible pathogenesis of SARS-COV-2 infection in a comprehensive manner and presents some medicinal plants of northeast India which possess therapeutic properties such as anti viral, antioxidant, immunomodulatory and anti-inflammatory activities which can help in combating the pathogenesis of COVID-19 infection. This review will open a window for the research and development of new plant based formulation as a mode of combination therapy that will support in treatment and management of COVID-19.

China reported the first case of a newly emerged novel corona virus from the city of Wuhan in December 2019 [WHO[95]]. Most scientists believed the virus to have a natural origin, and then transmitted from bats to humans, through pangolins and snakes as a result of zoonotic deluge in the seafood market of Wuhan[1,60]. However, a lab leak theory has not been completely ruled out. SARS-CoV-2 is a non segmented positive sense single stranded RNA virus with one of the largest viral RNA genome with ~ 30 kilobases and encodes about 29 viral proteins[11]. Major viral structural proteins include spike (S), membrane (M), nucleocaspid (N) and envelope (E). These structural proteins are responsible for the attachment of SARS-CoV-2 to the host's ACE2 receptor and entry into it. Most common mild symptomatic features include fever, cough, sore throat, diarrhea, shortness of breath and body pain, but in severe cases, it may cause pneumonia and even death[96]. There is no absolute treatment for COVID-19 but current clinical interventions are supportive and preventive in nature[74]. During initial wave of the pandemic, repurposed drugs, including Hydroxychlo-roquine, Lopanivir, Favipiravir etc were considered in early clinical trials. Currently, Remedesivir is the one of the highly explored antiviral agent across the globe. Other key players such as Tocilizumab, Dexame-thasone and Eculizumab are also added in the list[73]. With low loses and short term uses of corticosterioids and dexamethasone have aided in the COVID-19 management but flagrant misuse and high dependency on steroids has led to the exponential rise in secondary bacterial and fungal infections, mucormycosis being the most lethal one with a mortality rate of 40-50% [Tandon and Pandey[82]]. Considering the shortcomings associated with various antiviral drugs, *i.e.* long term antiviral drug exposure in immune-suppressed patients leads to the development of drug resistance, there is a dire need for search of plant derived natural products with antiviral activity that can be used as an alternative to synthetic antiviral drugs. Plant based antiviral compounds with remarkable therapeutic potentials against viral diseases is at the focal point of interdisciplinary medical research. The North-Eastern region of India is considered to be the treasure chest of medicinal and aromatic plants. It has India's richest repositories of plant diversity and holds around 50% of the country's total plant diversity[53]. The phytoactive agents found in the medicinal plants which can be utilized in the form of drugs as well as edible source has led to the current researches in medicinal plants for therapeutic alternatives. The unavailability of fully curative treatment of COVID-19 has compelled the researchers to look for alternative that can be used in dietary management as well as treating such infectious diseases. This review aims to summarize the pathogenesis of COVID-19 based on published clinical reports. This study also aimed to bring focus on edible medicinal plants possessing pharmacological and antiviral activities that can be used against different viral diseases as well as COVID-19.

Pathogenesis of SARS-CoV-2 :

COVID-19 caused by SARS-CoV-2 is a severe acute respiratory illness in human that have an average incubation period of 3-5 days[61]. Estimated mortality rate in the infected cases is about 6.6% which is lower than SARS-CoV [88]. Human angiotensin-converting-enzyme-2 (ACE-2) is the functional host receptor for SARS-CoV-2 that promotes viral entry through alveolar invasion. In addition, entry is facilitated by S protein priming associated with cellular serine protease called transmembrane serine protease 2 (TMPRSS2)[32]. TMPRSS2 causes proteolytic cleavage between S1 and S2 subunits. ACE-2 is highly expressed in lungs, kidney, small intestine, blood vessels, and heart. It possesses high binding affinity with SARS-CoV-2 spike glycoprotein than that of SARS-CoV, and virulence factors enter the host cell, causing severe infection. Thus, ACE-2 could be a potential drug target. After the viral entry, ACE-2 is cleaved by desintegrin and metalloproteinase domain 17 (ADAM17) at the ectodomain sites[108]. Shedding of receptor may lead to the loss of ACE-2 function. ACE-2, being a key modulator of rennin-angiotensin-system (RAS) causes the conversion of angiotensin I to angiotensin II thus, increases pulmonary vascular permeability[23]. In various studies, ACE-2 has been shown to play significant role in protecting against diseases like diabetes, hypertension and pulmonary diseases[86]. In cell cytoplasm, the viral RNA genome is released and replicated that leads to its multiplication and invasion in the nearby cells. It induces cellular responses resulting from surge of innate and adaptive immune cells. Among the innate immune cells, neutrophils are considered as one of the key factors that accelerates the progression of acute respiratory distress syndrome (ARDS)[28]. Although, T cells like cytotoxic CD8+ perform vital role in mitigating the virus, it also causes lung damage[16]. Elevated levels of monocytes and macrophages are related to the extensive increase in cytokines like interleukin (IL)-1, IL-6, IL-10 and tumor necrosis factor (TNF)α. This phenomenon is termed as cytokine storm[83]. Disruption of oxygen transport occurs as a result of inflammatory and apoptotic responses in the alveoli and causing ARDS. Circulation of inflammatory cytokines and chemokines are related to pulmonary inflammation and ARDS, which leads to the accumulation of pulmonary edema fluid in the air sacs of lungs. This disruption in gaseous exchange can cause respiratory failure or will result in multi-organ failure[84]. Mutation in SARS-CoV-2 spike protein D614G has shown to increase transmissibility and antigenicity[31].

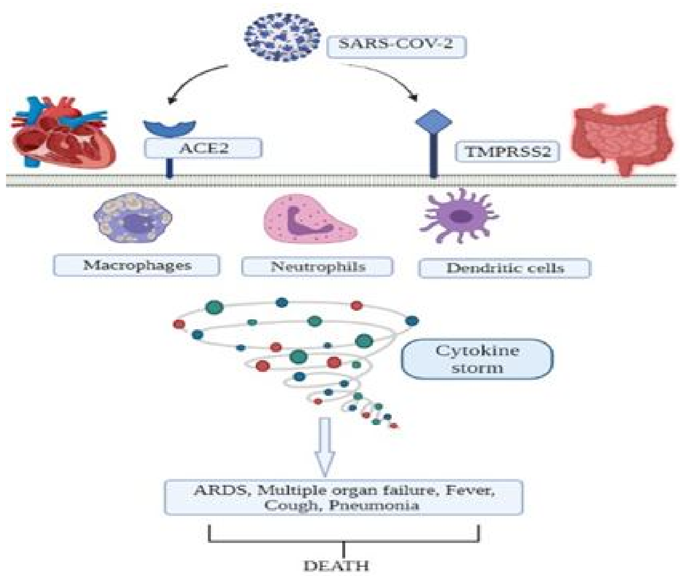

Figure 1. Shows pathogenesis of SARS-CoV-2 (created with biorender.com)

Table-1. Shows medicinal plants with anti-inflammatory properties.

Plant species	Common name	Activecompound/ Extract type	References
Curcuma longa L.	Turmeric, Haldi	Curcumin	Jurenka,[38]; Chainani-Wu *et al.*,[13]
Nigella sativa L.	Black cumin	Thymoquinone	Yimer *et al.*,[104]; Amin and Hosseinzadeh [4]
Zingiber officinale Roscoe	Ginger	6-Gingerol	Young *et al.*,[105]; Mashhadi *et al.*,[54]
Aegle marmelos (L.) Correa	Wood apple	Marmelosin	Pynam and Dharmesh,[70]; Rajaram *et al.*, [71]
Solanum nigrum L.	Black nightshade	Solanine	Piana *et al.*, [66]; Wang *et al.*,[94]
Allium sativum L.	Garlic	Allicin	Mrityunjaya *et a*l.,[58]; Arreola *et al.*, [5]
Abutilon indicum (Link) Sweet	Indian mallow	Whole plant ethanolic extract	Tripathi *et al.*, [89]
Mangifera indica L.	Mango	Mangiferin	Gong *et al.*, [26]; Oluwole and Esume,[62]
Ocimum sanctum L.	Tulsi	Eugenol	Prakash and Gupta,[69]; Godhwani *et al.*, [25]
Camellia sinensis (L.) Kuntze	Tea	Epigallocatechin gallate	Khalatbary and Ahmadvand,[42] Chattopadhyay *et al.*, [15]
Withania somnifera (L.) Dunal	Ashwagandha	Withaferin A	Logie and Vanden Berghe,[49]; Gupta and Singh,[29]
Moringa oleifera Lam.	Drumstick tree	Quercetin	Li *et al.*,[46]; Minaiyan *et al.*, [55]
Punica granatum L.	Pomegranate	Polyphenols	Yahfoufi *et al.*, [100]: Houston *et al.*, [33]
Artemisia annua L.	Sweet sagewort	Artemisinin	Uckun *et al.*,[90]; Kim *et al.*,[43]
Terminalia chebula Retz.	Black myrobalan	Hydroalcoholic fruit extract	Bag *et al.*,[7]; Yang *et al.*,[101]
Glycyrrhiza glabra L.	Liquorice	Glycyrrhizin	Akamatsu *et al.*,[3]; Yang *et al.*,[102]
Eclipta prostrata (L.) L.	False daisy	Dichloromethane extract	Tewtrakul *et al.*,[85]; Le *et al.*,[45]
Centella asiatica (L.) Urban	Indian pennywort	Titrated extract	Park *et al.*,[64]; Ju Ho *et al.*,[37]

Plants with anti-inflammatory activities :

Pathogenesis of COVID-19 is directly associated with inflammatory responses. Excessive amount of pro-inflammatory cytokines produced as a defense response leads to systemic inflammatory reactions. This is directly linked to mortality in COVID-19.

Table-2.Medicinal plants with antiviral properties

Sl. No.	Plant species	Common name	Type of virus against which it act	Reference
1	*Abutilon indicum.*	Indian mallow viruses	SARS-COV-2 and influenza	Chang *et al.*, [14]
2	*Aloe vera* (L.) Burm	Aloe vera, Ghritkumari	Influenza A virus	Choi *et al.*,[18]
3	*Azadirachta indica* A. Juss.	Indian lilac, Neem	Herplex simplex virus type-1 infection	Tiwari *et al.*,[87]
4	*Camellia sinenis*	Green tea, Common tea	Hepatitis B virus	Xu *et al.*,[99]
5	*Curcuma longa*	Turmeric, Haldi	Curcumin against Dengue virus, herpes simplex virus	Jennings and Parks,[36]
6	*Moringa oleifera* Lam.	Drumstick tree	Influenza A virus	Xiong *et al.*, [98]
7	*Momordica charantia* L.	Bitter gourd, Karela	Subtypes of influenza A virus	Pongthanapisith *et al.*,[68]
8	*Terminalia chebula*	Black myrobalan	Herpes simplex virus type-2	Kesharwani *et al.*, [41]
9	*Nigella sativa*	Black cumin Infection	Murine cytomegalovirus	Salem and Hossain,[76] 2000
10	*Commelina communis*	Asiatic dayflower	Influenza virus	Bing *et al.*,[9]
11	*Mangifera indica* L.	Mango	Mangiferin against herpes, simplex virus type 2	Zhu *et al.*, [107]
12	*Punica granatum*	Pomegranate	Influenza A virus	Moradi *et al.*,[57]
13	*Withania somnifera*	Ashwagandha	H1N1 influenza	Cai *et al.*,[10]
14	*Zingiber officinale*	Ginger	Chikungunya virus	Kaushik *et al.*,[40]
15	*Ocimum sanctum*	Tulsi	H9N2 virus	Ghoke *et al.*,[24]
16	*Phyllanthus emblica* L.	Indian gooseberry	Herpes simplex virus type 1 and type 2	Xiang *et al.*,[97]
17	*Psidium guajava* L.	Guava	H1N1 influenza virus	Sriwilaijaroen *et al.*,[81]

Uncontrolled inflammatory reactions can lead to development of cormorbidities[17]. Currently, synthetic medicines such as steroids, anti-inflammatory drugs, immunosuppressant, and IL-6 inhibitors are used to suppress inflammatory reactions but with associated adverse effects. Thus, there is an urgent need for natural anti-inflammatory products with high pharmacological properties with no or minimal side effects which can be extracted from medicinal plants[103].

Plants with anti-viral activities :

Many clinical studies have demonstrated the therapeutic potential of medicinal plants in treating infectious diseases[21]. For many years plants like *Allium sativum* (garlic) is widely used in traditional medicine as a prophylactic plant against viral diseases and also as food[6]. The organosulphur compounds (OSC) present in *A. sativum* are the main bioactive constituents and are also associated with its pungent smell[79]. Rouf *et al.*,[75] reported the antiviral activity of ginger against diseases caused by viruses such as severe acute respiratory syndrome coronavirus (SARS-CoV), herpes simplex virus-2 (HSV-2), rotavirus SA-11 (RV-SA-11), vaccinia virus (VV), newcastle disease virus (NDV), vesicular stomatitis virus (VSV) and reticuloendotheliosis virus (REV). Some of the anti-viral plants are listed in table-2.

Plants used for immunomodulatory properties:

Living beings are subjected to get traumas by diseases causing agents. Even the single celled microorganisms like bacteria have some sort of defense mechanism against infectious viruses[78]. The defense system becomes more complex in higher living organisms. In multicellular organisms, well established immune responses are generated by specialized immune cells provides protection from infective microorganism[19]. Some of the plant species from NE India having immunomodulatory properties are listed in table-3.

Plants with antioxidant activities :

Plants are considered as goldmine of natural form of exogenous antioxidants present in the form of phenolic compounds such as flavonoids, polyphenols and phenolic acid[67]. Plants possessing antioxidant activity are considered as pharmacologically significant because high oxidative stress leads to the development of comorbidities and life threatening diseases[39]. Oxidative stress leads to the accumulation of reactive oxygen species (ROS) which plays a deleterious role in tissues and is also associated with the development of diseases like cancer, neurodegenerative diseases, arthritis, and autoimmune disorders[65]. Drugs derived from medicinal herbs with anti-inflammatory, nephroprotective, antihyperlipidemic and antipyretic activities have been bestowed with antioxidants as part of their working mechanism[30]. Several mechanisms are present in the human body that can counter oxidative stress with the help of both endogenous and exogenous antioxidants which are produced either naturally or supplied through external source[47]. Natural and artificial food antioxidants are extensively used in dietary supplements and medicine particularly those containing fats and oils to safeguard the food from oxidation. Considering the minimal or no adverse effects in case of natural products, there is a decent shift in hunt for antioxidants which are found in nature. Several medicinal plants are reported to have antioxidant properties such as *Zingiber officinale*, *Withania somnifera*, *Cassia fistula*, *Morus alba*, *Carica papaya*, *Hibiscus sabdariffa*, *Nelumbo nucifera*, *Cynodon dactylon*, *Curcuma longa* and *Bacopa monniera*. Antioxidants from these plants have shown to act as oxygen scavenger with minimal or no side effects.

Table-3. Shows medicinal plants with immunomodulatory properties.

Sl.No.	Plant species	Common name	Reference
1	*Withania somnifera*	Ashwagandha	Davis and Kuttan,[20]
2	*Zingiber officinale*	Ginger	Carrasco *et al.*, [12]
3	*Nigella sativa*	Black cumin	Majdalawieh and Fayyad,[50]
4	*Ocimum sanctum*	Tulsi	Logambal *et al.*,[48]
5	*Olea europaea*	Olive	Vezza *et al.*, [92]
6	*Phyllanthus emblica*	Indian gooseberry	Huabprasert *et al.*,[34]
7	*Leucas aspera*	Tumba	Kurian *et al.*,[44]
8	*Carica papaya*	Paw paw	Mohamed,[56]
9	*Cassia occidentalis*	Coffee senna	Panigrahi *et al.*,[63]
10	*Moringa oleifera*	Drumstick tree	Nfambi *et al.*,[59]
11	*Phaseolus vulgaris*	Rajma, Bean	Wang *et al.*,[93]
12	*Areca nut*	Betel nut	Sari *et al.*,[77]
13	*Mangifera indica*	Mango	Makare *et al.*,[51]
14	*Artemsia annua*	Sweet sagewort	Islamuddin *et al.*,[35]
15	*Aegle marmelos*	Stone apple,bael	Govinda and Asdaq,[27]
16	*Asparagus racemosus*	Satawar	Gautam *et al.*,[22]
17	*Hibiscus sabdariffa*	Indian sorrel	Umeoguaju *et al.*,[91]
18	*Cynodon dactylon*	Bermuda grass	Mangathayaru *et al.*,[52]
19	*Morus alba*	Mulberry	Bharani *et al.*,[8]
20	*Vigna mungo*	Black gram	Solanki and Jain,[80]

Future prospects :

Due to the inefficiency and prevailing adverse effects on use of synthetic medicines in COVID-19 patients, so efforts have been made to fill up the void by giving special emphasis on medicinal plants with therapeutic properties. From ancient time, traditional healers have been passing on knowledge about the use of herbs. These data were usually unrecorded but currently, WHO recognizes that scientifically proven traditional and alternative and complementary medicines have many benefits. Data driven research of Traditional Chinese medicine (TCM) have already been carried out to identify potential treatment of COVID-19 [Ren *et al.*,[72]]. Prescription of Ayurvedic medicines prepared from medicinal plants and different approaches are being opted by the hospitals, mainly as adjuvant to synthetic medicines, which could be potentially beneficial in COVID-19 treatment[2]. China utilized a similar strategy during SARS crisis in 2003. Several Chinese herbal medicines were recommended for the patients infected with SARS-COV-2. The Ministry of AYUSH (Govt of India) promotes the use of plant based medicines such as AYUSH Kwath, AYUSH-64, Anuthaila, and Shamshamani vati. Medicinal plant extracts have shown significant anti-viral effects, which ranges from anti dengue to anti-influenza properties (Table 2). As efforts are underway to aid in treatment, caution must be considered against misguiding information about the effectiveness of certain plants which have not been scientifically investigated. Considering the current scenario of the pandemic COVID-19, scientific study and efficient research of medicinal plants can be imperative. Modern techniques associated with extraction of bioactive compound including decoction, maceration, soxhlet extraction, microwave–assisted extraction, percolation and pulsed electric field extraction[106]. These techniques could lead us to the discovery of novel bioactive compounds. Moreover, application of molecular docking approach in plant based drug discovery would add creamy layer of holistic insights into ethnobotanical research. Plant based products backed with robust clinical trials can add efficient data for future research.

Considering the global impact of COVID-19, it is the worst humanitarian crisis after World War II. It is caused by a highly infectious and mutable virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Vaccination and preventive measures are imperative in spreading of the disease. No therapy or drug is considered fully effective in the treatment. Currently, drug repurposing approach is being adopted in managing the disease. Synthetic medicines and repurposed drugs administered in the patients have shown detrimental effects which can lead to secondary infections. Thus, it is necessary to look out for alternate solutions. Since decades, natural products are explored for pharmacological research. Undoubtedly, plants are considered as rich source of bioactive compounds with antiviral properties. Natural products played significant role during previous pandemic outbreak like SARS-COV and MERS. Plants need to have anti viral, anti-inflammatory, anti oxidant, immonostimulatory, and ACE 2 inhibitory properties in order to be effective in the treatment of COVID-19. Furthermore, pathogenesis of the virus can be mitigated by combination therapy with plants having these pharmacological activities.

This review discusses several plant species of northeast India that are edible and also have potential pharmacological properties which can be utilized against COVID-19 research. Pathological manifestation of COVID-19 includes headache, sore throat, fever, cough, shortness of breath and neuroinvasion. Further scientific investigation and research is needed to understand the mode of action of active ingredients of plants and global research organization should generate effective strategies based of these pharmacological leads.

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Conflict of interest :

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