IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
November 2020 Vol.:19, Issue:4

Novel Coronavirus Emphasizing on Clinical Features, Virology, Management with Existing and Novel Treatments

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Parin Chokshi, Rahul Khemchandani, Ishani Patel, Rajashree Mashru*

Department of pharmacy, Faculty of pharmacy, Kalabhavan, The Maharaja Sayajirao University of Baroda, Vadodara 390001, Gujarat, India

Submission: 20 October 2020
Accepted: 27 October 2020
Published: 30 November 2020

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Epidemiology, Virology, Symptoms, Possible treatments and Prevention tactics

ABSTRACT

COVID-19, also known as the novel coronavirus-2019, is a new disease caused by SARS-CoV2. The World Health Organization has declared a global threat to the human environment due to its high contagious behaviour. In the current scenario about the increased risk of disease, various government and research institutes work for preventive measures. Based on present published evidence and facts, this review subsequently summarizes the etiology, virology of SARS-CoV-2, symptoms, pathophysiology, phase of COVID-19 infection, possible treatments, control, and prevention tactics. This review article will help to understand the novel coronavirus better and provide a reference for future studies.

INTRODUCTION:

The Novel Coronavirus-2019, also known as COVID-19, is a respiratory infection caused by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus) [(1)]. Initially, symptoms of SARS disease due to coronavirus (SARS-CoV) were detected in Southern China in the year 2003 through civet cats. Subsequently, in 2012 Saudi Arabia based Arabian camels were affected by respiratory syndrome due to coronavirus (MERS-CoV = Middle East Respiratory Syndrome). In December 2019, in China, SARS-CoV2 was detected, possibly from Bats or pangolins is still a matter of investigation. To date, COVID-19 has promptly spread in 215 countries with >1800000 confirmed cases causing more than 690000 deaths as of July 2020, considering a global threat (pandemic) by WHO (World Health Organization) [(1)] WHO recently confirmed SARS-CoV2 as "Airborne." It may be possible that the novel coronavirus can remain in the air in crowded indoor spaces [(2)].

ETIOLOGY:

Devastating coronavirus belongs to the family of enveloped, positive-sense, single-stranded RNA viruses. In normal circumstances, human beings suffered from mild upper respiratory diseases due to the tendency of coronavirus to attack over there. Till now, seven known species of coronavirus were found responsible for the conditions mentioned above. However, three known species of coronavirus can cause severe infection in human beings [(3, 4)]. COVID-19 belongs to the subfamily of Ortho coronaviridae from the family Coronaviridae, Order Nidovirales. The approximate size of the Novel SARS-CoV2-19 Variant is 125nm in diameter. It has got the most extensive genome range ranging from 26 to 32 kilo-bases among all RNA viruses identified till now [(3)]. Novel coronavirus contains four different structural proteins mentioned below,

- The nucleocapsid (N):-These proteins create a complex with host RNA and help the viral assembly after being replicated.

- Spike (S), Envelope (E), Membrane (M):- The mentioned three proteins are mainly responsible for creating the viral envelop. S Protein has a club-shaped surface projection, which establishes the characteristics of a virus, i.e., crown-like outlook observed through electron microscopy (Figure 1), creating the passage for the virus to enter the human cell [(3, 4)].

The virus tends to adhere to the receptor protein Angiotensin-Converting Enzyme 2 (ACE 2) of the host (human being cell) using its S protein. ACE 2 receptor is present in epithelial cells

of different parts of the human body like blood vessels, kidney, intestine, and most opulently in alveolar cells present in the human lungs. The virus causes a significant decline of ACE 2 in human cells, which finally damages the lungs [1, 3, 4]. COVID-19 also targets human enzyme Transmembrane Protease Serine 2 (TMPRSS 2) for priming its S Protein and also to contribute the fusion with the membrane of the host cell [1, 3, 4].

The initial discovery suggests that animals transmit the virus COVID-19 to humans [3,4]. Although the major spread of the virus is caused within human beings by symptoms like coughing, sneezing, and talking by the infected individuals thus, the inhalation of respiratory droplets is a major factor in the spread of the virus [3, 4].

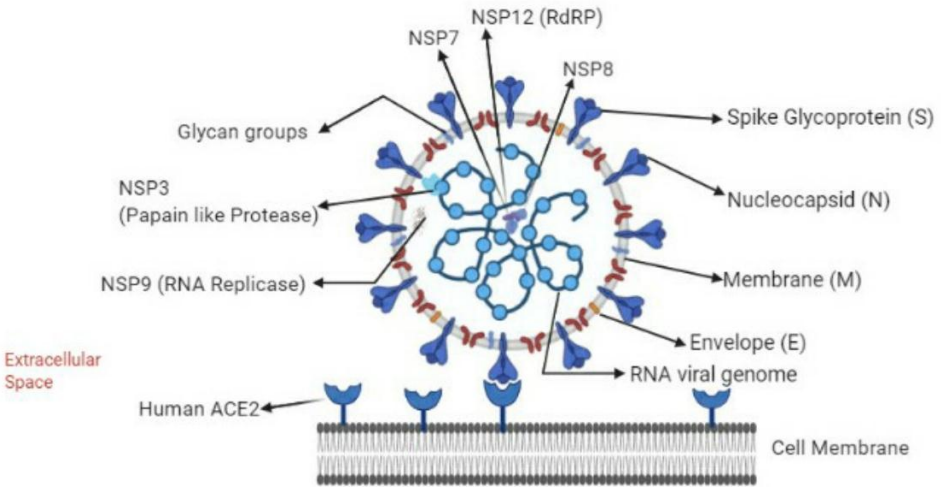

Figure No. 1: Novel SARS-CoV-2 [5, 6, 7]

EPIDEMIOLOGY:

The outbreak of coronavirus struck Wuhan city of China back at the end of November 2019, followed by an almost uncontrollable outburst during December 2019 [8]. Subsequently, taking advantage of continual ongoing traffic of human beings throughout the world, the virus has spread so rapidly and comprehensively, covering almost the entire globe [8].

VIROLOGY:

Coronavirus is non-segmented, enveloped, and positive-sense RNA genomes ranging from 26-32 kb extensively conveyed in people and mammals [5, 9].

To date, four genera of coronavirus are identified, namely α, β, γ, and δ. α and β are the two genres of COVID-19 responsible for transmitting the infection to humans [5].

Table 1[2] relates to coronavirus species for humans as hosts

Table No. 1: Several Coronavirus species for human as host [2, 5]

Host	Virus Species	Genre	Cellular Receptor
Human	HCoV-229E	α	Aminopeptidase N(APN)
	HCoV-NL63		Angiotensin-converting enzyme 2 (ACE2)
	HCoV-HKU1	β	Unknown
	HCoV-OC43		9-O-acetylated sialic acid
	SARS-CoV		Angiotensin-converting enzyme 2 (ACE2)

Coronavirus comprises of 6 Open Reading Frames (ORFs). The first ORF (ORF1a/b) occupies about two-thirds of the genome and encodes protein replicase (figure2a) [5]. Figure 3 depicts the entire genome structure of the coronavirus [6]. After a-1 frameshift signal, translation commences in ORF1a and continues in ORF1b. The big ORF1a and ORF1ab polypeptides, usually alluded to as pp1a and pp1ab, individually which are prepared primarily by the virally encoded Chymotrypsin-Like (CL) protease 3CLpro (likewise called M pro or principle protease) with extra cleavage achieved by a couple of viral papain-like proteases (PLPs), contingent upon the types of coronavirus [7]. About 33% of the genome encodes four auxiliary proteins: S, E, M, and N proteins. A subset of gathering two coronaviruses encodes an extra Haemagglutinin-Esterase (HE) protein (figure2a, 2b) [5]. The HE protein is involved with infection. HE protein is not required for replication, but essential to infect the natural host [7].

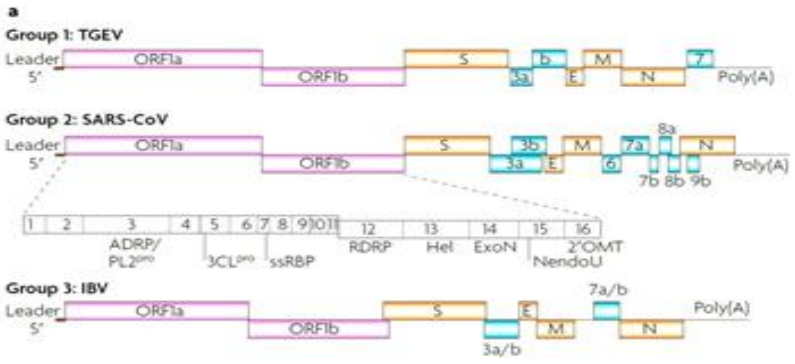

Figure No. 2: Assembly of the coronavirus genome [5].

Figure 2: Genomes representation of coronavirus from every group of coronavirus groups.

About the first two-thirds of the 26–32 Kb [3, 5], a positive-sense RNA genome encodes a large polyprotein (ORF1a/b; green) that is proteolytically cleaved to generate 15 or 16 non-structural proteins (nsps) for SARS-CoV2 [5]. The 3′-end of the genome encodes four structural proteins, namely S, M, E, and N (all demonstrated in blue) and a set of accessory proteins distinctive to each virus species (shown in red). Specific group 2 coronaviruses express an additional structural protein called HEs (not shown) [5].

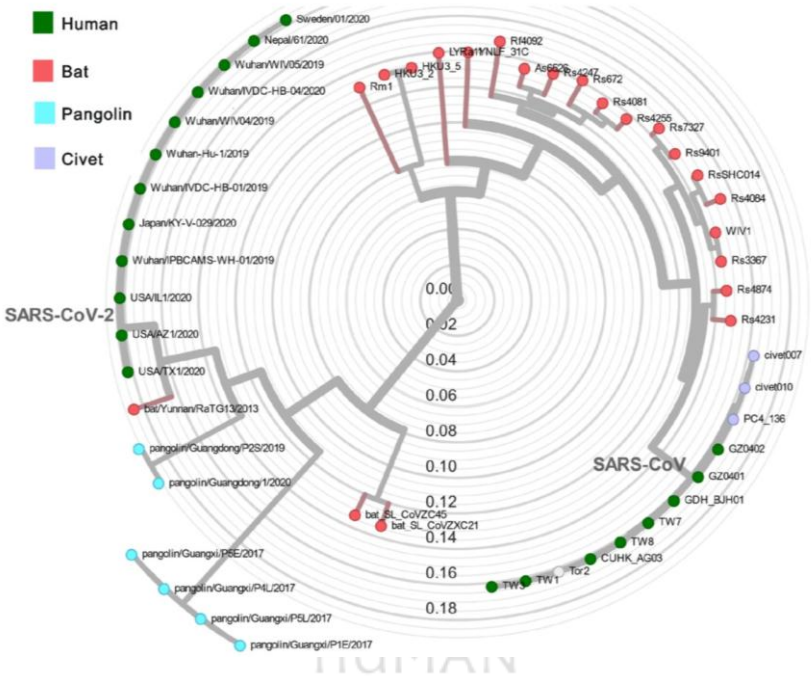

Figure No. 3: Genome structure for COVID-19 [6]

RNA replication is known to occur on Double Membrane Vesicles (DMVs) [10] (figure 4 [11] and figure 5 [12, 13, 14]). Recently combined genomic RNA is fuse into virions on layers situated between the Endoplasmic Reticulum (ER) and the Golgi apparatus known as ER-Golgi Transitional Compartment (ERGTC) [15]. Initial examinations proposed that these DMVs collect utilizing segments of the autophagy pathway [16]. However, another investigation suggested that replication continued typically, and generated DMVs macrophages lack ATG5, a principle element of auto-phagosomes [17]. The unfurled Protein Reaction (uPR) is initiated during coronavirus contaminations and might add to the DMV arrangement [18].

COVID-19 has similar homology (~80%) to SARS-CoV, which is responsible for Acute Respiratory Distress Syndrome (ARDS) and high mortality during 2002–2003 [19, 20].

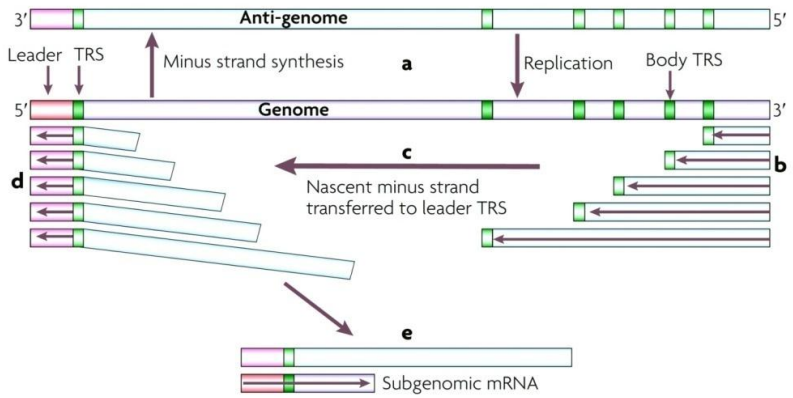

Figure No. 4: Mechanism for transcription and translation of coronavirus [11]

Figure 4: The above picture depicts the entry of the virus into the cell. The positive-sense RNA genome translated into replicase proteins from ORF1a/b. The full-length negative-sense RNAs are created with the help of above mentioned replicase protein, which subsequently serves as templates in creating additional full-length genomes (**a**) [11]. All Coronavirus m-RNAs contain a 5′ leader sequence fused to downstream gene sequences. These 5′ leader sequences add by discontinuing the synthesis of minus sense sub-genomic RNAs using genome RNA as a template. The Sub genomic RNAs are initiated at the 3′ end of the genome and proceed until they encounter one of the transcriptional regulatory sequences (TRS; red) that reside upstream of most open-reading frames (**b**) [11]. Through base-pairing interactions, the nascent transcript transfers to the complementary leader TRS (light red) (**c**) [11], and transcription continues with the help of the 5′ end of the genome (**d**) [11]. These sub-genomic RNAs then serve as templates for viral mRNA production (**e**) [11].

The COVID-19 genome encodes roughly 25 proteins that are necessary for the virus to infect humans and to do the replication (Figure 5). The spike (S) protein perceives human angiotensin-changing over compound 2 in the underlying phase of the disease; two proteases enzyme which cleaves to form viral and human proteins; the RNA polymerase, which arranges viral RNA; and the RNA dividing endoribonuclease [21].

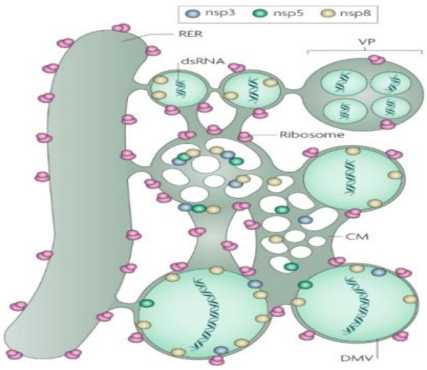

Figure 5: Variations in membrane induced by coronavirus as podiums for replicating the virus [12, 13, 14].

Figure5: COVID-19 infection encourages the development of a reticular replication network of modified membranes assumed to be the sites for replicating the virus. These alterations include Double Membrane Vesicles (DMVs), Vesicle Packets (VPs), Single Membrane Vesicles (SMVs), which are bounded by an outer membrane and Convoluted Membranes (CMs) that are interconnected and contiguous with the Rough Endoplasmic Reticulum (RER). Double-strand viral RNA is restricted in the inner part of DMVs and internal vesicles of the VPs, whereas CMs surround replicase proteins that are nsp3, nsp5, and nsp8 from which few nsp8 found inside the DMVs [12, 13, 14].

SYMPTOMS:

Symptoms for coronavirus required 10 to 14 days; this period is called an incubation period. Mainly two types of symptoms generally develop, which are flu-like symptoms and GIT infection. Table 2 [5, 6, 9] summarizes the symptoms related to COVID-19.

Table No. 2: Disease and symptoms related to COVID-19 [5, 6, 9]

Clinical Description	Common Cold	GIT Infection
	Sneezing, headache, fever, chills	Diarrhoea, gastroenteritis, enterocolitis
	SARS	COVID-19
	Temperature> 37.8°C, lethargy, sore throat, Muscular pain, symptoms like pneumonia, or breathing difficulty.	Fever, dry cough, lethargy, dehydration, high temperature, chest pain, breathlessness, haemolysis, pneumonia, multiple organ failure, or sometimes red rashes on the second finger of feet.

4 to 7 days (mean incubation period is 5.2 days) are generally required for the virus to incubate after those symptoms of infection appear [22]. The phase from the onset of COVID-19 symptoms to death ranged from 6 to 41 days, with a median of 14 days. This period is dependent on the age and immunity of the patient [22]. It was noted shorter among patients with >70 years of age as compared to the patients with age < 70 [23]. Fever, cough, runny nose, fatigue, sputum production, headache, diarrhoea, dyspnoea, and lymphopenia are frequently diagnosed symptoms in nearly 80% of patients at the onset of COVID-19 [22, 23, 24]. Clinical features discovered by a chest CT scan presented as pneumonia; however, abnormal features such as RNAaemia, Acute Respiratory Distress Syndrome (ARDS), acute cardiac injury, and incidence of grand-glass opacities which leads to the death of a patient [25]. (figure 6 represent the symptoms for coronavirus) [26].

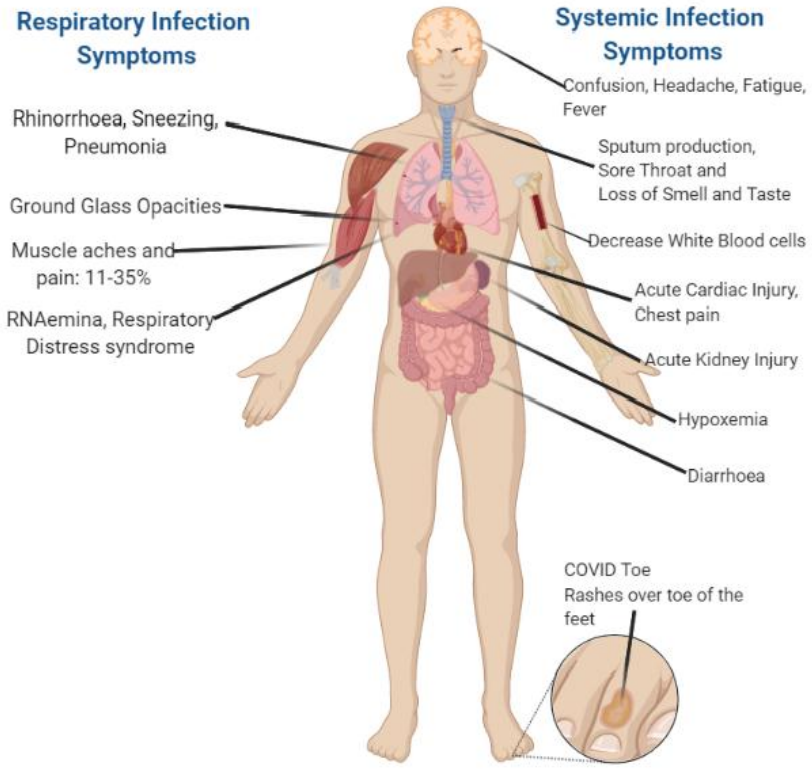

Figure No. 6: symptoms for coronavirus [26]

Coronavirus infected patients have increase leukocyte numbers, irregular respiration, and increased levels of proinflammatory cytokines. One of the COVID-19 case reports showed a patient at five days of fever presented with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C [25]. The sputum of the patient tested positive for COVID-19 when Real-Time Polymerase Chain Reaction (RTPCR) test was conducted. The laboratory findings presented leucopenia with leukocyte counts of 2.91 × 10^9 cells/L, amongst which

70.0% were neutrophils along with an increase of 16.16 mg/L of blood C-reactive protein, which was above the normal range (0-10 mg/L). Elevated levels of Erythrocyte Sedimentation Rate (ESR) and D-dimer were also detected [25, 26].

Mutation in COVID-19:

Two strains were recognized to have extreme COVID-19 disease are [25,26],

(1) L-strain

(2) S-strain

Both the strain ('L-strain' and 'S-strain') represent ancestries of the infection from Wuhan; the 'L-strain' experienced changes and transform into the S-strain [26]. The L-strain was found "forceful" in its spread (non-destructive).

Strains are named clades when there is a transformation that amino acid experiences in the external structure of the infection [26]. The names of clades are given by GISAID (Global Initiative on Sharing All Influenza Data), which is an open and universal collective action to share zoonotic flu-related genome sequence (and now, SARS-CoV-2 groupings) [26].

'L-type' and 'S-type' share a similar clade, 'S.' 'S' clade manages the variety in a quality called ORF8; therefore, this transformation is called ORF8-L84S, which is responsible for changing amino acid to Serine (S) from Leucine (L) [26].

Clades follow fixed naming structures: For ORF8-L84S, the ORF8 quality experienced a change in amino acid L at the 84th position of the quality's protein into the amino acid S [26].

Recent discovery had identified two different clades which are,

Clade 'G': Variation in a quality 'S' (disconnected to serine) changes at 614th position of aspartic acid (D) to quality's protein to glycine(G). Along these lines, the variation or clade 'G' is called S-D614G [26].

Clade 'V': Named NS3-G251V, valine (V) changes from NS3 quality glycine (G) located at position 251 [26].

Every single other transformation is named 'Other' or 'O' in GISAID, which incorporates changes like ORF8-S84L, where S and L transform the other way as well [26].

A change at 614th situation of the Spike protein (D614G) is quickly getting predominant and could make the infection gradually more destructive. The D614G strain is 10 times more infectious than the original Wuhan strain. The D614G strain was found in Malaysia in July-2020. The D614G transformation produces a new serine protease cleavage site close to its S1-S2 intersection of the spike protein. With a mixture of a nucleotide cancellation (delC) allele present in specific individuals accelerates the spread of infection into people [27]. This change can cause challenges in the conclusion of COVID-19 disease and creating immunization for COVID-19 contamination [27].

A recent finding suggests that almost half of the coronavirus strains in India show "Spike" or "D614G" transformation [28].

COVID-19 PATHOPHYSIOLOGY:

The mechanism of COVID-19 infection occurs in the following steps:

(Overall pathophysiology of COVID-19 shown in figure7) [29]

1. Invasion and replication of coronavirus

2. Presentation of antigen in coronavirus infection

3. Humoral and cellular immunity (Host response)

4. Cytokine storm in COVID-19

5. Coronavirus immune evasion (escape)

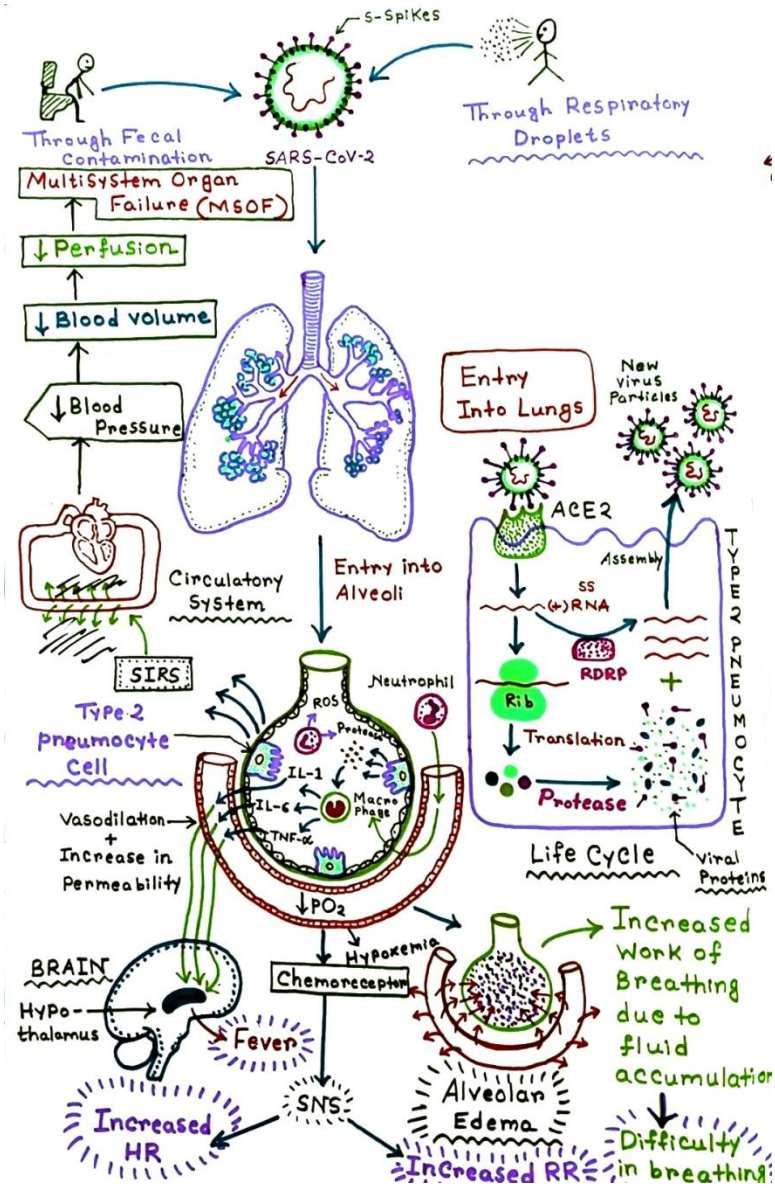

Figure No. 7: Pathophysiology of COVID-19 [29]

1. Invasion and replication of coronavirus:

The existing pattern of the infection with the host comprises the accompanying five stages: attachment, penetration, biosynthesis, maturation, and release. First of all, the virus bind to host receptors (attachment). Then the virus enters the host cells through endocytosis or membrane fusion (penetration) and releases the viral substances into the host cells. The viral RNA enters the nucleus for replication of viral proteins (biosynthesis). Then, new viral particles are made (maturation) and released [30]. Spike protein made from transmembrane trimetric glycoprotein projecting out from the viral surface decides the type of coronaviruses

and host tropism. Spike protein includes two suitable subunits, namely the S1 subunit and the S2 subunit.

S1 subunit is responsible for controlling the host cell receptor.

S2 subunit is responsible for the fusion of viral components and cellular membranes.

The spike protein for SARS-CoV-2 binds to Angiotensin-converting enzyme 2 (ACE2) [31, 32, 33]. Following the authoritative of SARS-CoV-2 to the host protein, the spike protein undergoes protease cleavage at S1/S2 sites [35, 36, 37, 38]. After the division at the S1/S2 site, S1 and S2 subunits remain non-covalently bound, and the distal S1 subunit adds to the adjacent of the layer to S2 subunit at the prefusion state [33]. Subsequent cleavage at the S2 site probably enacts the spike for film combination through irreversible, conformational changes [39]. The coronavirus has a furin cleavage site ("RPPA" succession) at the S1/S2 site. This site is exposed to cleavage during biosynthesis in a radical differentiation to the SARS-CoV [33]. However, the S1/S2 site was likewise presented to division by different proteases [38,40]. The universal articulation of furin made this infection exceptionally pathogenic. Figure 8 depicts the replication of disease [41].

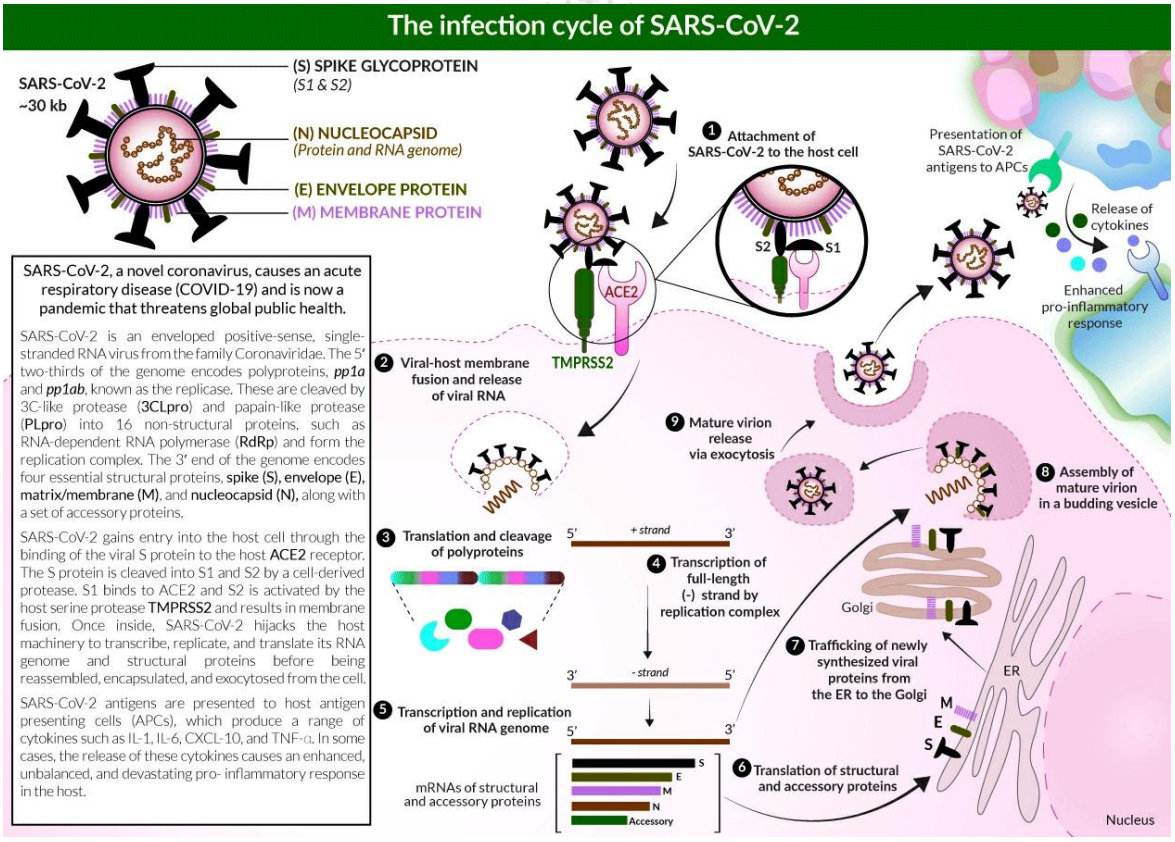

Figure No. 8: Replication of Infection into the host cell [41]

2. Presentation of antigen in coronavirus infection:

When the coronavirus enters the cells, antigens express the Antigen Presentation Cells (APC). Antigenic peptides represent Major Histocompatibility Complex (MHC; or Human Leukocyte Antigen (HLA) in humans) and then recognized by virus-specific Cytotoxic T Lymphocytes (CTLs). Therefore, understanding of antigen presentation of SARS-CoV-2 will be beneficial in understanding the pathogenesis of COVID-19 [46]. The antigen presentation of SARS-CoV principally depends upon MHC I and MHC II molecules [42]. Earlier research demonstrates various HLA polymorphisms that correlate to the susceptibility of SARS-CoV, such as HLA-B∗4601, HLA-B∗0703, HLA-DR B1∗1202and HLA-Cw∗0801 [43, 44]. In contrast, the HLA-DR0301, HLA-Cw1502, and HLA-A∗0201 alleles protect from SARS infection [45]. HLA-DRB1∗11:01 and HLA-DQB1∗02:0, which are MHC II molecules that are more susceptible to MERS-CoV infection [46, 47].

3. Humoral and cellular immunity (Host response):

The distinguishing feature between SARS and MERS pathogenesis is the significant rise in interleukin-1β (IL-1β), interferon-γ (IFN-γ), Interferon-inducible Protein-10 (IP-10), and Monocyte Chemo-attractant Protein-1 (MCP-1) in the blood of patients affected with COVID-19 [24].

Epithelial cells, Dendritic Cells (DCs), and alveolar macrophages are three principle segments for intrinsic insusceptibility in the aviation route [48]. Dendritic cells and macrophages are the natural, safe cells that help to fight against infections until Adaptive Immunity is achieved [48].

CD4+ and CD8+ T cells play a vital role in moving APCs towards depleting lymph nodes where viral antigen are present to T cells [49]. B cells are activated by CD4+ T cells in promoting the production of virus-specific antibodies, whereas virus-infected cells remove CD8+ T cells. Patients with a severe infection presented with the history of lymphopenia, a reduced number of peripheral T blood cells, and raised several proinflammatory cytokines [50, 51, 52].

In the early phase of COVID-19, dendritic cells and epithelial cells activate. A cluster of proinflammatory cytokines and chemokines including IL-1β, IL-2, IL-6, IL-8, both IFN-α/ β, TNF, C-C subject chemokine 3 (CCL3), CCL5, CCL2, and IP-10, etc. are expressed which are controlled by the immune system of the host cells. The high levels of these chemokines

and cytokines contribute to developing the disease [53, 54, 55]. T-helper-2 cells (Th2) produced IL-10, which helps in decreasing cytokines and chemokines to reduce the severity of infection [56, 57]. [Figure 9 [58, 59] and figure 10a and figure 10b [60]]

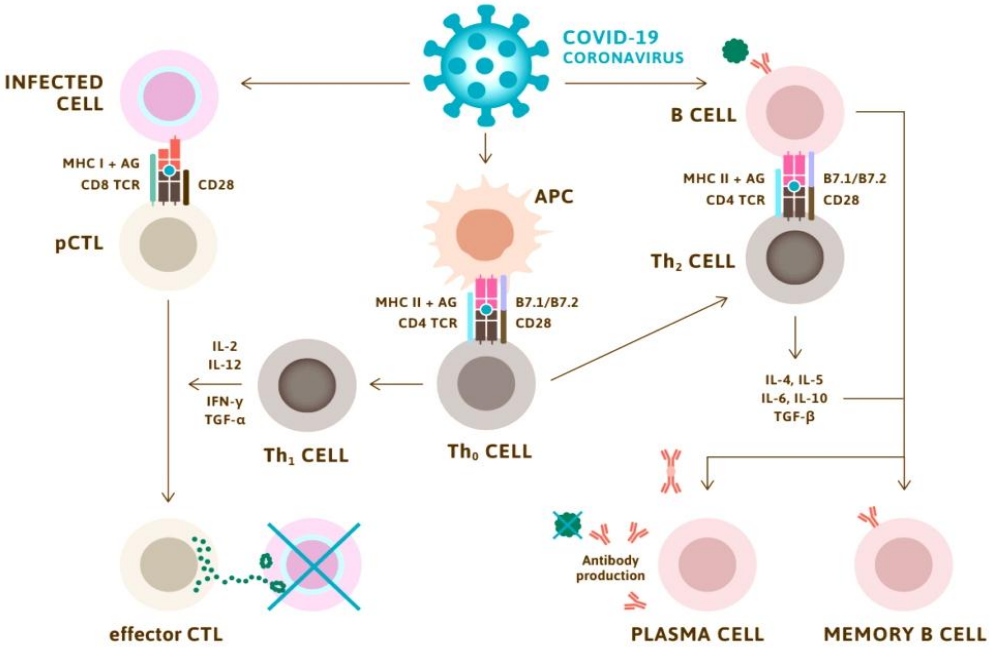

Figure No. 9: Adaptive immune response against Covid-19[58, 59]

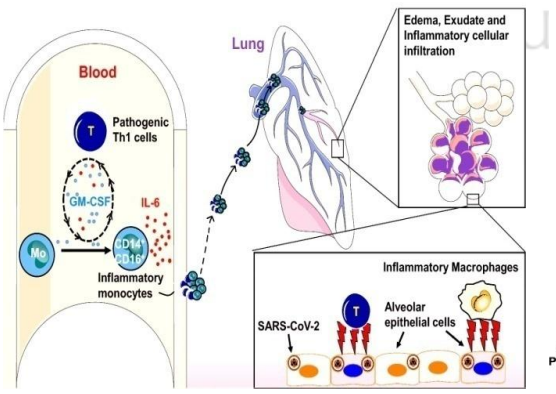

Figure No. 10(a): Host alveolar response against COVID-19 [60]

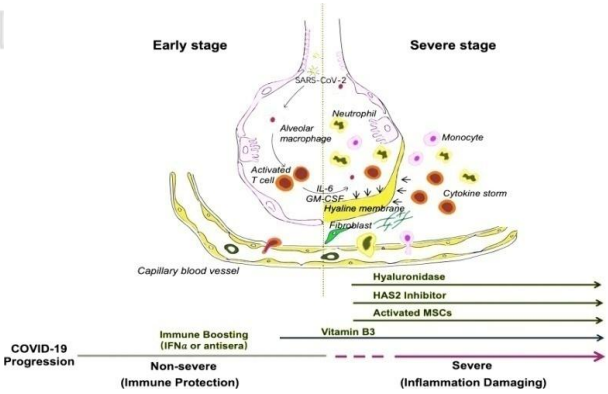

Figure No. 10(b): Immune response at alveoli against COVID-19 [60]

4. Cytokine storm in COVID-19

Acute Respiratory Disease Syndrome (ARDS) is the principal cause of mortality in the Novel coronavirus 2019. Among 41 SARS-CoV-2-infected patients, six died from ARDS [24]. For

SARS-CoV-2, SARS-CoV, and MERS-CoV infections, ARDS is the shared immunological event [61]. Cytokine storm is the primary mechanism for ARDS to occur, which is a result of an uncontrollable release of proinflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, etc.) and chemokine (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells in SARS-CoV infection [24, 62, 63, 64]. Those with SARS-CoV individuals have high levels of IL-6, IFN-α, and CCL5, CXCL8, CXCL-10 in serum compared to those with mild to moderate disease [65]. The cytokine storm will trigger a massive attack by the immune system to the body responsible for the occurrence of ARDS and multiple organ failure that ultimately leads to death in a severe case of SARS-CoV-2 infection [61]. Figure 11 represents the cytokine storm for COVID-19 [66].

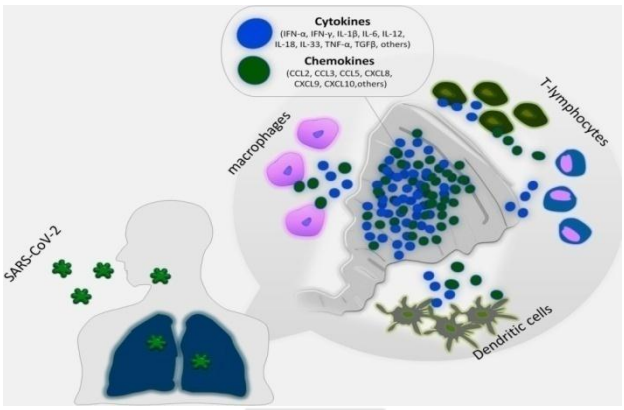

Figure No. 11: Cytokine storm for COVID-19 [60]

5. Coronavirus immune evasion (escape):

The evolutionarily conserved microbial structures called Pathogen Associated Molecular Patterns (PAMPs) were recognized by Pattern Recognition Receptors (PRRs) [67]. However, SARS-CoV and MERS-CoV can induce the production of double-membrane vesicles that need PRRs and later replicate these vesicles along these lines evading the host location of their dsRNA [67]. IFN-I(IFN-α and IFN-β) protectively affect SARS-CoV and MERS-CoV contamination, yet the IFN-I pathway is repressed in infected mice [68, 69]. Accessory protein 4a of MERS-CoV may block the induction of IFN at the level of MDA5 activation through direct interaction with double-stranded RNA [70]. ORF4a, ORF4b, ORF5, and membrane proteins of MERS-CoV inhibit nuclear transport of IFN Regulatory Factor 3 (IRF3) and activation of IFN β promoter [71, 72, 73].

In addition to IFN, multiple chemokine and cytokines are induced as part of the host response to coronaviruses such as MHV, SARS-CoV, and FIPV. SARS patients detected a rise in the

levels of cytokines (IL-1, IL-6, and IL-12) and chemokines (IL-8, CCL2, and CXCL10) [73,74]. Genomics and proteomics discovered that IFNα, IFNβ, IFN-γ, and chemokines such as CXCL10 and CCL2 levels increase early after the onset of infection in most of the patients and groups of chemokines and interleukins reduce in the recovered patients to have robust anti-virus antibody response [74]. However, levels of CXCL10, CCL2, and other pro-inflammatory mediators remained elevated, and anti-SARS-CoV antibody titres were low in those patients who developed severe disease. SARS-CoV-infected pulmonary epithelial cells were the source of cytokines and chemokines such as CCL2, IL-6, IL-1β, and TNF [75]. Others have suggested that a strong TH2 (IL4, IL-5, and IL-10) response correlated with a poor outcome [76, 77].

Table No. 3: Various phase of COVID-19 infection [40, 78, 79, 80, 81]

Stage	Name of Phase	Duration	Features
1	Asymptomatic phase	1-2 days	A virus starts replicating once it binds to the epithelial cells in the nasal cavity when air containing a virus is inhaled. At this stage, the throat and nasal swabs help to detect the virus. During this stage, viral load may be low, but this type of patient carries infections. The RT-PCR value for the viral RNA can help in predicting viral load and spread of disease.
2	Upper airway and conducting airway response	3-7 days	The virus circulates and travels down the respiratory tract via conducting airways and alveoli. Nasal swabs or sputum should yield the virus and early markers of the innate immune response leading to an increase in CXCL10, IFNβ, and IFNγ. The disease will be mild and mostly restricted to the upper and conducting airways in 80% of the infected patients.
3	Hypoxia, ground glass pulmonary	>7 days	Pulmonary infiltrates and hypoxia will develop to almost 20% of the infected patients leading to stage 3 disease. Nearly 2% of the fatality rate is estimated

	infiltrates, and progression to ARDS		in stage 3 conditions, which can vary with age. Geriatric individuals are at high risk of infection due to low immune response and less ability to repair the damaged epithelial cells. The elderly also reduces mucociliary clearance allowing the virus to spread more quickly in the alveolar sac of the lungs.

Table No. 4: Classification of COVID-19 patient [82]

Sr. No.	Phase	Features/Symptoms
1	Asymptomatic	COVID nucleic acid test positive. Without any clinical symptoms with a healthy chest image.
2	Mild	Symptoms of Acute Upper Respiratory Tract Infection (AURTI) such as fever, fatigue, myalgia, cough, painful throat, runny nose, and sneezing. Digestive symptoms, such as nausea, vomiting, abdominal discomfort, and diarrhoea.
3	Moderate	Pneumonia, recurrent fever, cough with no obvious hypoxemia, and chest scan with lesions.
4	Severe	The patient developed pneumonia and hypoxemia with $SpO_2 < 92\%$.
5	Critical	ARDS may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction, and acute kidney injury.

Treatment Possibilities:

Probable treatment and management options for COVID-19 are mentioned below in Table 5 and Table 6, which include Allopathic, Ayurvedic, Homeopathy, Siddha, Unani medications, and Vaccines development.

(Figure 12)

Table No. 5: Possible Allopathic treatments for COVID-19

Sr. No.	Drug Name / Therapy	Possible mechanism of action	Dose	Adverse effect	Reference
1	Hydroxychloroquine (HCQ) and chloroquine (CQ)	SARS-CoV-2 enters cells by binding to the ACE-2 receptor, and HCQ or CQ prevents the virus from binding with the ACE-2 receptor by inhibiting terminal glycosylation [83]. HCQ and CQ avoid the binding of SARS-CoV-2 with gangliosides, which inhibit contact with the ACE-2 receptor [84]. As weak bases, both the drugs gathered in an acidic environment inside the lysosomes. These drugs interfere with lysosomal activity and autophagy to inhibit MHC class II and antigen presentation to inhibit immune activation [85]. CQ and HCQ also interfere with TLR signalling by changing pH and direct binding to nucleic acids. Cytokine production stimulates through the TLR signal pathway; thus, CQ and HCQ inhibit various	The initial dose of 400 mg to 800 mg HCQ two times a day and a maintenance dose of 200 mg twice a day for four days.	CQ and HCQ have adverse effects such as GI upset and headache. Other adverse effects are due to chronic drug therapy, which includes cardiac arrhythmia, retinopathy, and prolongation of the QT interval. CQ is generally less tolerable than HCQ and can cause acute poisoning at a lower dose	83, 84, 85, 86.

		cytokines such as IL- 1, IL- 6, TNF, and IFNγ by mononuclear cells [86].		[86].	
2	Remdesivir	Inhibit RNA dependent viral RNA polymerase of SARS CoV-2.	The initial dose of 200 mg followed a maintenance dose of 100 mg for 9 days.	Hepatoxicity at high dose, Nausea, and Vomiting.	87
3	Lopinavir + Ritonavir	Lopinavir and Ritonavir are HIV protease inhibitors that inhibit 3-chymotrypsin-like protease for coronavirus.	400 mg + 100 mg for 6 days	Abdominal pain, vomiting, nausea, hepatotoxicity, and dyslipidemia.	88
4	Nafamostat + Camostat	The combination acts as a Serine Protease Inhibitor, which is essential for binding of Spike protein binding.	600 mg + 300 mg for 7 days	Nausea and vomiting	89
5	Famotidine	Famotidine is a Protease and Cytokine inhibitor.	150 mg IV approx.	Constipation, diarrhoea, joint pain, and mood swings.	90,91,92
6	Umifenovir	Viricidal activity interferes with a lipophilic membrane	Not Known	Nausea, vomiting.	93

		of the virus.			
7	Nitazoxanide	It blocks the maturation of the viral nucleocapsid N protein, helping for the production of viral particles.	600 mg of dose two times a day, for 5 days.	Diarrhoea, abdominal pain, nausea, and vomiting.	94
8	Azithromycin	Increase level of interferon (IFN)	500 mg for the first day, followed by 250 mg of dose for 2 to 5 days	Abdominal pain, vomiting, and diarrhoea.	95
9	Ivermectin	It Binds and destabilizes the cell-transport proteins that are required to enter the nucleus.	30-50 mg	Diarrhoea, Vomiting, loss of appetite, diarrhoea, and nausea.	96
10	Interferon α/β	IFNs-α/β are broad-spectrum antivirals that exhibit both direct inhibitory effects on replication of the virus and support an immune response for virus infection clearance.	10 mIU/mL	Itching, Dry mouth, Abdominal pain	97
11	Corticosteroids (Dexamethasone)	Immunomodulatory action, anti-inflammatory action, and believed to ramp down the excessive inflammatory	6 mg dose once daily for 10 days (seriously	Gastric upset and Tachycardia.	98

		response (cytokine storm).	ill patient)		
12	Favipiravir	Favipiravir converts into phosphoribosylated form (favipiravir-RTP) in cells and recognized as a substrate by viral RNA polymerase for inhibiting RNA polymerase activity of the coronavirus.	The initial dose of 1800 mg two times a day on day 1, followed by a maintenance dose of 800 mg two times a day for 14 days.	Reduced RBC production, and increase in liver function parameters (Aspartate Amino Transferase (AST), Alkaline Phosphatase (ALP), Alanine Amino Transferase (ALT), and total bilirubin. Increased vacuolization in hepatocytes. Teratogenic and testies related toxicity.	99,100,101,102
13	Itolizumab and Tocilizumab	Itolizumab is a humanized recombinant IgG1 and CD6 monoclonal antibody which	1600 mg/day.	Nausea, rash, urticaria, flushing,	103,104,105, 106

		targets the extracellular, Scavenger Receptor Cysteine Rich (SRCR) distal domain 1 of CD6 cell. It is a novel biological agent approved in India for the treatment of psoriasis. CD6 is a costimulatory molecule required for optimal T-cell stimulation by the APCs is crucial in T-cell proliferation to form Th1 and Th17 cells. DCGI (Drug Controller General of India) approved it for restricted emergency use in COVID-19 treatment. These two drugs are withdrawn from the market for use in COVID-19 as the medicine has failed to meet the primary requirement in phase III clinical trials [107].		cough, wheezing, dyspnea, dizziness, and headache.	
14	Convalescent plasma Therapy (CP)	Plasma collected from COVID-19 individuals, transfused into infected patients as postexposure prophylaxis. CP is a passive antibody therapy that can neutralize the virus by preventing replication or binding without interfering	One dose of 200 to 400 mL of CP obtained from recently recovered donner with neutralizing	Not described	108, 109

		with replication.	antibody titers above 1:640 was transferred.		

Table No. 6: Future Scope for vaccine and drug development [110]:

Name	Feature	Current status
Intranasal Vaccine (chAd-SARS-CoV-2-S)	Adenovirus vectored the intranasal vaccine, which encodes pre-fusion stabilized spike protein (ChAd-SARS-CoV-2-S). This one-shot of the vaccine induces a high level of neutralizing antibodies, promotes mucosal IgA and T cell response, and prevents SARS-CoV-2 infection in the Upper and Lower respiratory tract [111].	Completed pre-clinical studies in a chimpanzee [111].
Sputnik-V vaccine (viral vector vaccine)	The Gameleya research institute develops this vaccine in collaboration with the Russian defence ministry. The vaccine is administered in two dese and consists of two stereotypes of human adenovirus, each carrying S-antigen [112, 113]. It is said to produce an immune response for up to 2 years [112, 113].	Government plans for mass production in October [112].
Oxford University Vaccine (ChAdOx1 nCoV-19)	The Jenner Institute and Oxford Vaccine Group at the University of Oxford developed this vaccine. After vaccination, the SARS-CoV-2 surface spike protein is produced, which alerts the immune system to attack COVID-19	British pharma company AstraZeneca is developing vaccine incorporation with Oxford University. They said it was "on track" to roll around two billion doses in September [114].

	[114].	Now approved for phase II and Phase III clinical trials in India as positive results for phase I clinical trial studies were positive [114].
Moderna RNA Vaccines (mRNA1273)	The Moderna vaccine based on a novel approach, wherein scientist injects the specially designed mRNA (genetic material) which produces viral protein or antigen. The antigen triggers the immune system, thereby helping the body to defend itself against COVID-19 [115].	Entered in Phase II and Phase III clinical trials [115].
Pfizer vaccine	Pfizer and its German partner BioNTech are working on four vaccine candidates, each representing a different combination of messenger RNA method and target antigen [116].	Now in Phase II and Phase III trials [116].
Sinovac Biotech Vaccine	The vaccine is known as Coronavac, developed by Sinovac Biotech Ltd. (Beijing, China), a biopharmaceutical company [117].	Now in Phase II and Phase III trials [117].
Bharat biotech vaccine (Covaxin)	Also known as inactivated virus vaccine developed by Bharat biotech India	Phase II and Phase III trials [118, 119].
Zydus Cadila vaccine	Zydus Cadila is working on two vaccine candidates. One candidate makes use of a live measles virus strain against COVID-19, and other deals with the development of a DNA vaccine against coronavirus membrane protein, which would trigger a robust immune response and destroy the viral cells [119].	Currently, in Phase 1/ 2 trials [119].
LY-CoV555 (Eli-Lilly and	It's a potent neutralizing IgG1 monoclonal antibody (mAb) designed to act against the spike protein of SARS-	Currently, in the Phase 3 trials [120, 121].

AbCellera)	CoV-2. It blocks viral attachment and entry into human cells and neutralizing the virus that potentially prevents and treats the patients [120, 121].	
Antibody (CT-P59) Celltrion Inc., the Korean company	CT-P59 works by neutralizing the virulent D614G variant of COVID-19, the variant associated with increased viral transmission and widespread of the virus.	Currently, in the Phase 1 trial [122, 123].
Hyperimmune Globin (Takeda, CSL, and Others)	A type of plasma-derived therapy product - is designed to give a patient passive immunity against a specific disease. The plasma-derived form recovered patients would be channelled to developed hyperimmune Globin in combination with the novel drug candidate, TAK-888 [124].	Currently, in the Phase 3 trial [124].
MK-4482 (Merck & Co., Ridgeback)	MK-4482 is commonly known as EIDD-2801. The oral drug given in capsule is a prodrug of synthetic nucleoside derivative of N4-hydroxycytidine, which exerts antiviral activity by disrupting the viral RNA replication [125].	Currently, in the Phase 2 trial [125].
Janus Kinase signal transducer and activator of transcription (JAK-STAT) pathway inhibitor	JAK inhibitors reduce the clinical symptoms in multiple organs in the late inflammatory phase to reduce the cytokine storm [126]. Example: Tofacitinib (JAK1,2,3); Methotrexate (JAK1-2, Tyk2);	New proposed pathway [126]

Table No. 7: A most promising treatment for COVID-19

Drug or Treatment	Clinical Phase	New or Repurposed	Emergency use
Antibody (CT-P59)	1	New	x
Antibody (LYCoV555)	3	New	x
Convalescent Plasma	2/3	New	x
Dexamethasone	4	Repurposed	x
Hyperimmune Globin	3	New	x
Interferon (Rebif)	3	Repurposed	x
Oral antiviral (MK-4482)	2	Repurposed	x
Hydroxychloroquine	Approved	Repurposed	x
Favipiravir	Approved	Repurposed	x
Remdesivir	3	Repurposed	✓

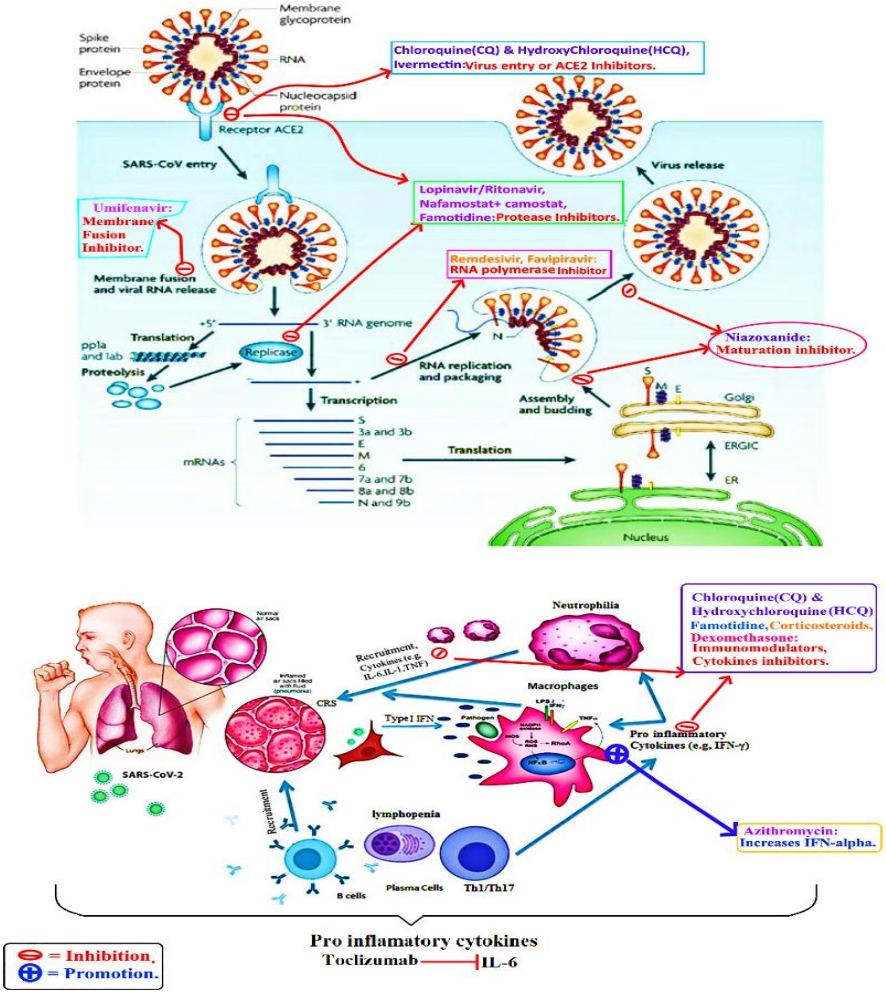

Figure No. 12: mechanism action of various possible drugs for treating COVID-19 [127].

Possible Herbal or Ayurvedic treatment:

Ayurveda is practiced since ancient times and has proven potential to several diseases such as pain killers, flu, migraine, and many more. As per recent findings for COVID-19 several mechanisms of action have been reported for Virus infection. Some possible natural remedies derived from herbal plants and minerals have proven beneficial in the prevention and treatment of COVID-19 disease.

Herbal medicines:

According to recent findings for coronavirus based on its mechanism of action, several herbal medications can prove beneficial, this herbal and polyherbal medication are described briefly:

(a). Angiotensin-Converting Enzyme Inhibitors (ACEIs):

These herbal herbs act by preventing binding and penetration of virus to epithelial cells.

1. **Ginger (Zingiber officinale; Family: Zingiberaceae):**

The rhizome of ginger has demonstrated a beneficial role in health management since ancient times and has proven chemo-preventive agents. Zingiberene is an active constituent of ginger. Zingiberene ($C_{15}H_{24}$) is a monocyclic sesquiterpene with three isoprene units capable of suppressing ACE receptors [128, 129, 130, 131].

Ginger additionally contains other therapeutically active compounds like Gingerol and its related compounds, Zingerone, Shogoal, and Paradol [128, 129].

Ginger has antioxidant activity, anti-inflammatory activity, and prevents macromolecular damage caused by free radicals/oxidative stress and also has anti-inflammatory action as well [131].

2. **Yohimbine (Pausinystaliayohimbe Pierre; Family: Rubiaceae):**

Yohimbine is the primary alkaloid obtained from the bark of West-African Pausinystaliayohimbe Pierre. Yohimbine has adrenergic-2-receptor antagonism property, serotonin receptor antagonist, and antagonistic activity against ACE receptors [132, 133, 134].

(b). Immunomodulatory agents and Protease inhibitors:

COVID-19 positive patients secret a high amount of various inflammatory cytokines.

Inflammatory cytokines are soluble proteins secreted by particular (effector) cells that play a central role in inflammation (increased expression of adhesion molecules and induction of inflammatory cells) and tissue repair (angiogenesis, epithelial growth, and modulation of fibroblast). Inflammatory Cytokines (ICs) display elevated ARDS in patients [135, 136].

1. Giloy (Tinospora cordifolia; Family: Menispermaceae):

Giloy is a potent immunomodulator that protects from various infections having protease inhibition activity against the virus [137]. Giloy contains 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonacin, Cordifolioside A, Magnoflorine, Tinocordiside, and Syringin as the main active constituent. This constituent makes giloy cytotoxic and potent immunomodulators [138, 139].

Giloy inhibits pro-inflammatory cytokines like TNF-a and different Interleukins [140].

2. Kalmegh (Andrographis paniculata; Family Acanthaceae):

Kalmegh is a medicinal plant that has significant constituents such as Diterpenoids, Flavonoids, and Polyphenols. Andrographolide is a principal active constituent of kalmegh, which has anti-inflammatory, antibacterial, and hepatoprotective [141, 142, 143].

Andrographolide inhibits the production of Proinflammatory cytokines like *IFN*-γ, *TNF*-α, IL-2, and IL-12, which are responsible for the rise of immature DCs tolerogenic properties [144]. NF-*κ*B plays a significant role in inflammatory pathogenesis by promoting various medicines designed to treat human inflammatory disease to inhibit the activation of NF-*κ*B [145, 146, 147, 148].

Andrographolide decrease inflammation by inhibiting NF-kappa B activation through the covalent modification of reduced Cys62 of p50 [149], andrographolide formed a covalent bond with a reduced cysteine of p50 to block the binding of NF-κB oligonucleotide to nuclear proteins. It suppressed the activation of NF-κB in stimulated endothelial cells to reduce the expression of cell adhesion molecule E-selectin and preventing E-selectin-mediated leukocyte adhesion underflow [149, 150]. Andrographolide is also active against COVID-19 by inhibiting the Main binding protease (M^{pro}), which is involved in the release of polypeptides that are functionally extensive proteolysis and the enzyme's cleavage itself from the genome, pp1a and ppa1ab sites [151].

3. Ashwagandha (Withaniasomnifera; Family: Solanaceae):

Ashwagandha contains active chemical constituents like Alkaloids (Isopelletierine, Anaferine, Cuseohygrine, Anahygrine, etc.), Steroidal lactones (Withanolides, Withaferins), and Saponins. Most of it has an immunomodulatory effect [152].

Ashwagandha inhibits lipopolysaccharide S-induced proinflammatory mediators like TNF-α, IL-1β, and IL-12. Ashwagandha was effective in modulating cytokines of both Th1 (IFN-γ, IL-2) and Th2 (IL-4) profiles [152]. Ashwagandha increases Th1 activity and increases the CD4+ and CD8+ counts with the speedy recovery of CD4+T cells in immune-suppressed animals. Ashwagandha selectively stimulates Th1 immunity by increasing the secretion of IFN-γ and IL-2 [153]. Ashwagandha kills viruses by inhibiting Viral DNA polymerase [154].

COVID-19 binds to the ACE-2 receptor of the host cell through its spike protein called as Receptor Binding Domain (RBD). Ashwagandha has an inhibitory or antagonistic effect against ACE 2 receptors proving beneficial against COVID-19 [155].

4. AYUSH-64:

The AYUSH Ministry of India developed an anti-malarial drug that is under trial for use in COVID-19. AYUSH-64 has anti-inflammatory and immunomodulatory activity.

It consists of the following plants:

a. Saptaparna Stem bark (Alstonia sholaris)

b. Katuki root (Picrorhiza kurroa)

c. Chirayata whole plant (Swertia chirata)

d. Kuberaksha seed (Caesalpinia crista) [156]

The aqueous bark extract of **Alstonia sholaris** in BALB/c mouse induced the cellular immune response at 50mg/kg body weight once a day for seven consecutive days, whereas at 100mg/kg body weight inhibited the delayed type of hypersensitivity reaction [157]. Indole alkaloids demonstrated down-regulation of inflammatory cells, cytokines (IL-6), and also the balance of antioxidants. Total alkaloids present in the Saptaparna stem bark inhibits the production of inflammatory cytokines TNF-α and IL-8 in lung and bronchoalveolar lavage fluid [158, 159].

The **Picrorhiza kurroa** rhizome has shown the activity of improving the immune response in mice by increasing the proliferation of lymphocytes and cytokine levels (IL-4 and IFN-γ) in serum [160]. Pre-treatment with Picrorhizakurroa rhizome extract exhibited anti-inflammatory activity by suppressing macrophage-derived cytokines (TNF-α, IL-1β, IL-6, IL-10) and mediators via suppression of NF-κB signaling [161]. Picroside-II is an active ingredient of Picrorhiza Scrophulariiflora showed the promising effects of anti-inflammation in cells and animals by decreasing the concentrations of TNF-α, IL-1β, and IL-6. It also suppressed the activation of the P65 NF-κB signalling pathway [162, 163].

The whole plant of **Swertia chirata** inhibits NF-κB/DNA interactions and conjointly proinflammatory IL-8 expression in cystic fibrosis cells at IC_{50} concentrations [164]. Bellidifolin and Swerchirin are the two significant xanthones obtain from the plant of Swertiachirata, which are known for the inhibition of proinflammatory cytokines, IL-6, and TNF-α. Bellidifolin potently inhibits the Prostaglandin E_2 (PGE_2) by suppressing the protein expression of Cyclooxygenase-2 (COX-2) [165]. The crude extract of Swertia chirata plant showed antiviral properties against Herpes simplex virus type-1 [166, 167].

The seed of **Caesalpinia crista** is responsible for reducing the activity of TNF- α, IL-1β, and IL-6 mRNA expression in the hippocampus and the frontal cortex brain areas in rats [168]. the seed extract of C. bonducella produced dose-dependent increases antibody production and delayed-type allergic reaction in rats indicating promising immunostimulant properties [169]. The ethanolic seed extract of C. bonducella seeds in Albino rats showed anti-inflammatory, antipyretic, and analgesic properties [170, 171]. Endospermic seeds of C. bonducella demonstrated immunostimulant activity by activation of splenocytes and thymocytes [172].

5. Gokhru (Tribulus terrestris; Family: Zygophyllaceae):

The main active constituent of gokhru is Terrestreamine having an inhibitory effect against Protease [173].

6. Garlic (Allium sativum; Family: Amaryllidaceae):

The presence of organosulfur (Alline), Flavonoids (Anthocyanins), and Flavanols are linked to the medicinal property of the Allium species [174]. Enzyme alliinase converts Alline into Allicin. The flavour of garlic is due to Allicin. Allicin converts into Di-Allyl

Sulfide (DAS), Di-Allyl Di-Sulfide (DADS), Di-Allyl Tri-Sulfide (DATS), and Di-Allyl-Tetra-Sulfide (DATTS) [175].

Organosulfur compounds such as Allicin, DATS, and Ajoene is the principal constituent associated with the antiviral activity of garlic [176]. Compounds like DADS, DAS, and Alliin significantly reduced inflammation during dengue attack [177, 178].

Allicin can penetrate through the phospholipid membrane of the cell and can contribute to the inhibition of viral multiplication [179]. Allicin can modulate the immune response against viral infection and blocks the discharge of proinflammatory cytokines such as IL-6 and TNF-α [179]. This suppression of cytokines was also conjointly substantiated in an experimental study on Reticulo-Endotheliosis virus-infected cells [180]. In addition to inhibiting cytokines, Allicin can alter the transcription of the NF-κB and binding activity of DNA. It also blocks the expression of NF-κB mediated inflammatory target genes. Allicin encompasses a high quantity of selenium and sulphur responsible for the antioxidant effect by reacting with intracellular thiol compounds [181].

7. Quercetin-onion (Allium cepa; Family: Amaryllidaceae):

Onion contains quercetin and kaempferol as main flavanols. These compounds affect the growth of many viruses [182, 183]. Onion extracts are effective in diminishing infection of viruses by blocking the attachment of the virus with the viral cell. This antiviral property in onion is similar to quercetin, zalcitabine, allicin, and ribavirin [182, 183, 184, 185].

The entry of viruses into the cell is inhibited by quercetin, which interacts with Haemagglutinin protein [186]. Quercetin blocks the stage of viral attachment of viral infection to reduce the contamination of Enterovirus [187]. The derivative of quercetin that is quercetin 3-O-D-glucoside, targets the entry of the Ebola virus in the host cell [188].

Quercetin inhibits the translation of poliovirus RNA by blocking the process of forming multiple copies of polio-virus using the minus-RNA strand [189]. Quercetin inhibits the hepatitis C virus translation process [190]. SARS-CoV protease inhibits the presence of quercetin, which is necessary for the replication of the SARS virus [191]. Scientists observed that quercetin derivatives increase zinc uptake necessary to inhibit RNA Polymerases [192, 193, 194]. Quercetin induces mitochondrial biogenesis in a host cell, essential for lowering the susceptibility to influenza A virus infection [195, 196]. Quercetin also inhibits the Human Immunodeficiency Virus-1 (HIV-1) integrase and reverse transcriptase enzymes in HIV

infected cell [197, 198]. Quercetin inhibits RNA polymerase activation by reducing polyprotein synthesis by Rhinovirus proteases [199].

Quercetin can change the activities of proinflammatory cytokines in dengue virus-infected cells [200]. The presence of Quercetin could increase phosphorylation of Eukaryotic Initiation Factor 2α (eIF2α) in response to virus infection and thereby prevent viral replication. Hence the application of quercetin in the host cells in enhancing the immune response [201, 202]. Quercetin has the potential to reduce the cleavage of eIFG4II and decrease the formation of viral capsid protein [203].

Mechanism of quercetin in host cell:

The inhibition of virus in host cells by quercetin involves the following steps [204].

1) Attachment of virus on the host cell membrane

2) Virus entry in a host cell

3) Reverse transcription

4) Replication of virus genetic material

5) Transcription

6) Translation

7) Viral assembly.

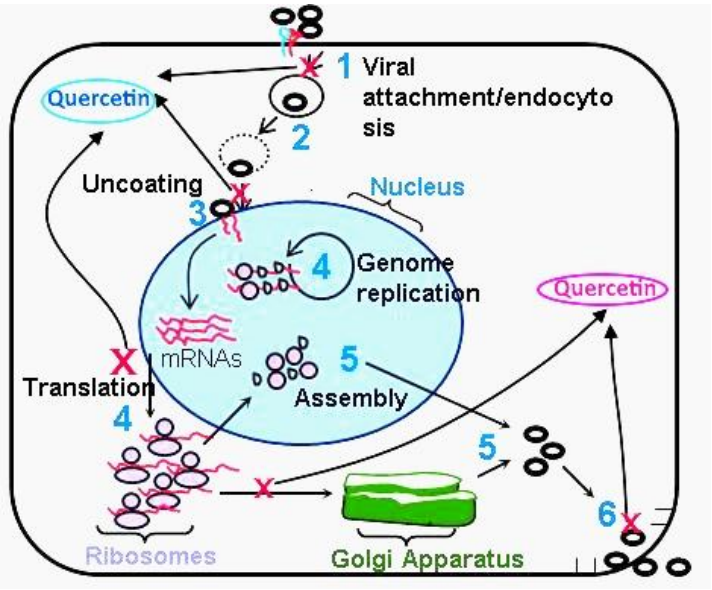

Figure No. 13: Mechanism action of Quercetin [198]

8. Curcumin-Turmeric (Curcuma longa; Family: Zingiberaceae):

"Indian saffron" is the other name of turmeric because of its bright yellow colour, found on the lands of the Indian subcontinent and Southeast Asia, has more than two centuries of scientific history [205]. Non-volatile oils, volatile oils, minerals, carbohydrates, curcuminoids, proteins, and fats are present in various proportions in the ground dried root of turmeric [205]. Commercially available turmeric is a mixture of three molecules, collectively known as curcuminoids. Curcuminoids contain curcumin (60–70%), demethoxycurcumin (20–27%), and bisdemethoxycurcumin (10–15%) along with sesquiterpenes, diterpenes, and triterpenoids [206, 207].

Curcumin inhibits the immunomodulatory effect of DCs and interferes in the maturation of myeloid DC, leading to the suppression of CD80 and CD86 expression [208]. These two co-working membrane proteins provide a stimulating signal required to activate T-cells [208]. The damage in the production of proinflammatory cytokine (IL-12) is due to the inhibition of the Mitogen-Activated Protein Kinase (MAPK) activation and translocation of NF-κB [209], which would raise the amount of IgM and IgG antibodies [210].

The JAK/STAT signalling pathway is offended by the Suppressor of Cytokine Signalling Proteins (SOCS) responsible for controlling proinflammatory proteins and cytokines development [211]. Curcumin potently inhibits LPS induced expression of IL-6, TNF-α, and prostaglandin-endoperoxide synthase two mRNA in macrophages by preventing the inhibition of SOCS1 and SOCS3 [212]. Curcumin further inhibits LPS induced p38 MAPK activation by reducing its phosphorylation and nuclear translocation [211, 213]. These data support the liability of pure curcumin to increase the expression of SOCS1 and SOCS3 proteins in primary myeloproliferative neoplasms cells by blocking class-I histone deacetylases (In particular HDAC8 activity) [213].

In addition to JAK/STAT, another important molecular pathway involved in inflammation is NF-κB [214]. The transcription factor NF-κB regulates the inflammatory response and homeostasis of the immune structure [213, 214]. Curcumin effectively reduces the LPS induced release of NO and proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as iNOS expression and NF-κB activation [213, 214].

9. Echinacea (Echinacea Species; Family: Asteraceae):

Echinacea is a genus of nine herbaceous flowering plants belonging from the daisy family, usually referred to as coneflowers from eastern and central North America [215]. Three species of Echinacea, namely E. purpura, E. angustifolia, and E. Pallid, used Echinacea in the treatment of Respiratory Tract Infections (RTI) and inflammatory conditions, including the common cold, coughs, bronchitis, and inflammation of mouth and pharynx in Native America from centuries [215]. Echinacea is known for its immunostimulant activity, anti-inflammatory, anti-viral, and anti-microbial [216, 217, 218]. The immunomodulatory effects of Echinacea are due to an increase in the innate and specific immunity [218].

It has an Immunostimulant activity triggered mainly by increased synthesis of IL-1β, IL-6, IL-12p70, TNF-α, and NO. It exhibits its behaviour by modulating pathways of JNK, p38 MAPK, and NF-κB [219, 220, 221].

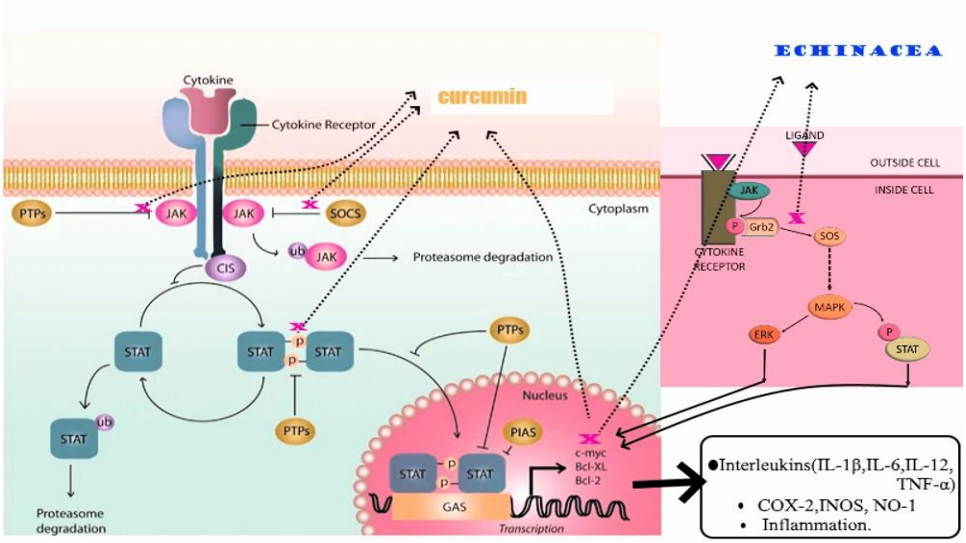

Figure No. 14: Pathways for the immunomodulatory and inflammatory activity of curcumin and Echinacea [222].

Figure 14: A pictorial representation of the major molecular pathways linked to immunomodulatory and inflammatory activities controlled by Curcumin and Echinacea. The line with red colour indicates the activation pathway, while the red dotted line indicates the inhibition pathway.

10. Tulsi (Ocimum sanctum; Family: Lamiaceae):

It increases the production of a T-dependent cellular immune response. It enhances the production of Th1 cytokines, IL-2, TNF-α, IFN-γ, and Th2 cytokine [223].

It has an antiviral effect as well [224].

11. Liquorice (Glycyrrhiza glabra; Family: Fabaceae):

Liquorice contains flavonoids such as iso-flavonoids, formononetin, liquiritin, saponin, triterpenes (liquirtic acid, glycyrrhizin) [225, 226]. Liquorice also contains sugars, coumarins, amino acids, starch, tannins, phytosterols, choline, and vitamins (e.g., Vitamin C) [225, 226, 227, 228]. About 25% of the liquorice root extract contains glycyrrhizin [229]. Glycyrrhizin contains one molecule of glycyrrhetinic acid and two molecules of glucuronic acid [228].

The activation of NF-κB and p38/ERK MAPK signalling is inhibited by lipopolysaccharide in a dose-dependent manner to prevent the inflammatory response [229, 230]. Liquochalcone-A present in liquorice root prevents cellular oxidation [231]. Liquorice flavonoids induce a pro-inflammatory action by interfering with the NF-κB signalling pathway to stop the release of inflammatory cytokines. Glycyrrhizic acid, liquiritinc acid, and liquiritigenin decrease proinflammatory cytokines such as IL-1β, IL-6, and TNF-α in the liver and block the release of multiple inflammatory mediators synthesized by activated macrophages [231, 232, 233, 234]. Glycyrrhizic acid inhibits PGE2 formation, COX activity, and inhibits the platelet aggregation and inflammatory factors [228, 230, 231, 232, 233, 234].

Glycyrrhetinic acid has many beneficial pharmacological effects, likewise an immunomodulatory effect and synthesis of interleukins [233, 234, 235] with corresponding antibody output, INF-γ, and T-cells signifying its antiviral property [236, 237].

12. Cinnamon bark (Cinnamon zeylanicum; Family: Lauraceae):

Cinnamon bark is commonly known as taj in India, known to have an inhibitory activity of CD3 activated T cells, decreases the levels of IFN-γ, and inhibits the cytokines activation pathways by inhibiting the activation of p38, JNK, ERK1/2, and STAT4 [238].

13. Oregano (Oreganum species; Family: Lamiaceae):

Commonly known as Ajwain, in India is found to decrease TNF-α, IL-12 and increases the impact of Transforming Growth Factor-β (TGF-β) [239].

Oregano contains essential oil, Carvacrol, which has significant immunomodulatory activity [240]. It also decreases the raised levels of various proinflammatory cytokines, including IL-4, IL-12 [240].

14. Peppermint (Mentha species; Family: *Lamiaceae)***:**

Mentha species decreases pro-inflammatory mediators and cytokines, including Nitric Oxide, TNF-α, IL-6, IL-4, IL-10, and PGE2 [241, 242].

Mentha species contains Menthol and Menthanonethat are known to impart anti-viral and immunomodulatory effects [241, 242].

15. Vitamin-C (Citrus species; Family: Rutaceae):

Vitamin C regulates distinct genes expressed in human macrophages that are induced by Lipo Poly Saccharide (LPS) through the NF-κB-light chain enhancer of activated B cells [243], which reduces the secretion of proinflammatory cytokines (IL-6 and TNF-α) [244].

Vitamin C promotes the production of T cells in human peripheral lymphocytes [245, 246]. In vitamin C, human IL-2 generating T cells decreased, while TNF-α and IFN-γ expressing T lymphocytes were not affected [244, 245, 246]. High levels of vitamin C (0.3mM to 0.5 mM) have reduced the feasibility and release of T cells to decrease proinflammatory and anti-inflammatory cytokines (TNF-α, IFN-γ, and IL-4 by activated T cells) [247].

16. Clove (Syzygium aromaticum; Family: Myrtaceae):

Clove contains a high amount of eugenol (50–87%), eugenyl acetate, tannin, thymol, and β-caryophyllene [248].

Clove reduces the synthesis of NO Expression [249]. Clove tends to decrease the production of pre inflammatory cytokines like TNF-α, IFN-γ, IL-4, IL-6, IL-10, and IL-12 [250, 251].

17. Amla (Phyllanthus emblica L; Family: Phyllanthaceae):

Amla contains a raised amount of Vitamin C (100-900 mg/gm), Ellagic acid, emblicol, gallic acid, phyllemblic acid, quercetin, kaempferol, etc. [252]. The significant pharmacological activity of amla is due to isphyllembin.

It reduces LPS-induced inflammation, iNOS, COX-2, and NF-κB [253]. It reduces the production and secretion of proinflammatory cytokines like MIP-2, TNF-α, IL-6, and IL-1β in lung tissue [254].

18. Sacred herb Eriodictyol- (Eriodictyon californicum; Family: Boraginaceae):

It has an immunomodulatory effect through the Regulation of the Nrf2 pathway and inhibits inflammatory cytokines TNF-α, IL-6, IL-1β [255, 256].

19. Luteolin- flavonoids found naturally in celery, thyme, green peppers, and chamomile tea:

The levels of TNF-α, KC (CXCL1), Intercellular Adhesion Molecule-1 (ICAM-1), and Superoxide Dismutase (SOD) is reduced by chamomile tea. Activations of MAPK and NF-κB pathways and neutrophils inflammation is reduced by chamomile tea. It reduces pulmonary haemorrhage and neutrophilic inflammation and interstitial oedema [257]. The suppression of pulmonary inflammation minimizes the level of cytokines, such as TNF-α, KC, and ICAM-1 content in the Broncho Alveolar Lavage Fluid (BALF) [257].

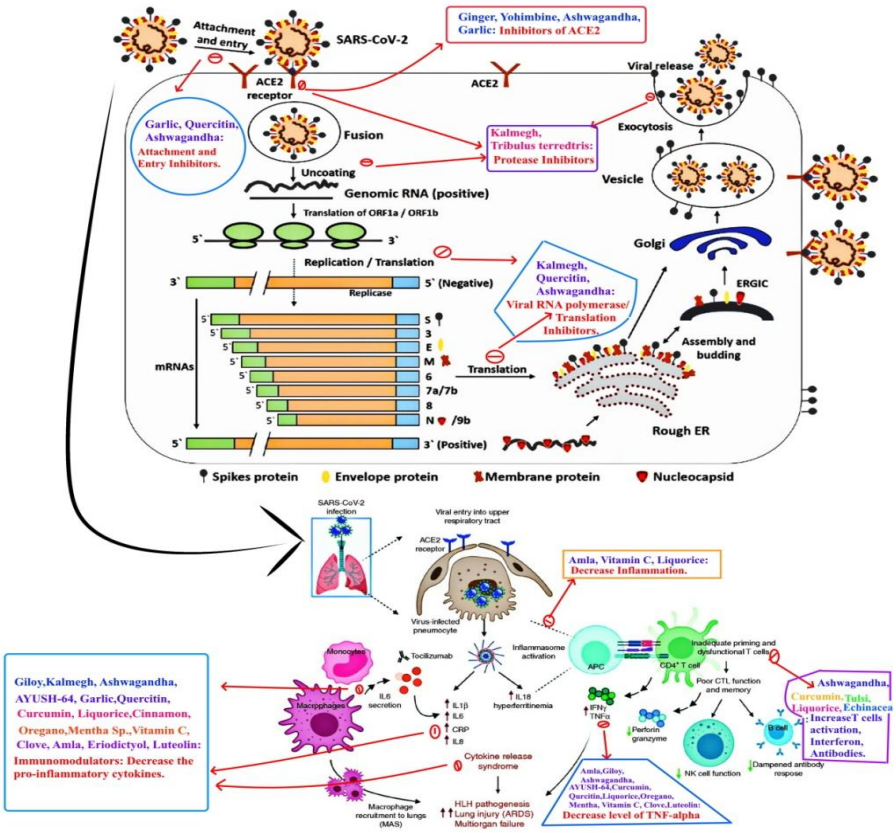

Figure No. 15: Mechanism of action of various natural plants against COVID-19 infection [127].

20. Available marketed ayurvedic formulations under trial that claimed to be effective against COVID-19:

A. ZingiVir-H tablets: The Clinical Trial Registry of India (CTRI) has approved an Ayurvedic formulation developed by the Pankajakasthuri Herbal Research Foundation in Kerala has agreed for a clinical trial for the treatment against COVID-19. Clinical trials of the Zingivir-H tablet showed significant results against respiratory infections, viral fever, and acute viral bronchitis, Respiratory Syncytial Virus, and Influenza virus. ZingiVir-H contains seven ingredients, including herbs and minerals [258, 259].

It has the following actions against the virus:

1. Inhibiting viral attachment/entry
2. Inhibiting viral replication/multiplication/translation
3. Inactivation of proteases thus the destruction of the virus
4. Increase the synthesis of interferon-alpha [258, 259].

B. Coronil:

Patanjali Ayurveda medicines developed this coronil medication. It is an "Immunity Booster" medicine useful in the management of COVID-19 infection [260].

It contains three components:

1) Coronil vati
2) Swasari vati
3) Anu taila [260, 261].

Table No. 8: Composition of Coronil [260, 261, 262]

Composition of various formulations of Coronil		
1. Coronil Vati	**2. Swasari Vati**	**3. Anu Taila**
• Ashwagandha	• Mulethi	• Jivanti

• GIloy • Tulsi	• Kakdasingi • Rudanti • Sounth • Marich • Choti pipal • Lavang • Dalchini • Akarkara • Abhrak bhasma • Nukta shukti bhasma • Godanti bhasma • Kapardhak bhasma • Praval Pishthi • Sphatik bhasma • Tankan bhasma	• Nagarmotha • Jala Devdaru • Dalchini • Sevya • Swet Chandan • Anantmool • Plawa • Mulethi • Daru haldi • Agaru • Plawa • Bel • Satavari • Punnarnahawa • Brahati • Utpala • Surbhi • Kantkari • Brhati • Prashanprani • Ruti • Vidang

		• Tej patra • Renuka • Kamala Kinjala • Ajadugdha • Till taila

C. Ayush Kwath Powder:

Zandu Pharmacy developed herbal immunity booster formulation recommended by the Ministry of Ayush India. It mainly contains powder of Tulsi, Tvak, black pepper, and dry ginger. This powder is administered in hot water by adding lemon and natural jaggery two times a day [263].

Some natural medicines derived from Unani Siddha and Homeopathy which are effective against COVID-19 infection:

Table No. 9: Natural medicines from Unani, Siddha, and Homeopathy system of medicine:

Sr. No.	Plant/Drug name	System	Mechanism of action	Dose
1	Arsenicum album 30	Homeopathy	It has an inhibitory effect on NF-κB hyperactivity and reduced expression of reporter gene GFP in transfecting HT29 cells, and inhibition of TNF-α [264]. Restoration of DNA damage of liver and kidney and its	Daily once in an empty stomach for 3 days. (Should be repeated after 1 month till the Infection persists) [266].

			protein [265].	
2	Bryonia alba L.	Homeopathy	Anti-inflammatory, decrease cough and reduce inflammation of the lungs [266].	As directed by the physician
3	Nilavembu kudineer (NVK) Zingiber officinale / Chukku kappi, Piper longum / Thippili, Syzygium aromaticum / Kirambu, Anacyclus pyrethrum/ Akkirakaram, Tragus involucrate / Hygrophila auriculata/ Terminalia chebula / Kadukkai, Justicia adhatoda / Anisochilus carnosus/ Karpooravalli, Costus speciosus / Koshtam, Tinospora cordifolia / Seendhil, clerodendrum serratum / Siruthekku, Andrographis paniculata /Cyperus rotundus / Sidaacuta / Vattathiruppi ver/ Korai kizhangu / Neermulli ver.	Siddha	The immunomodulatory effect, health tonic, antipyretic, analgesics, antioxidant, antiviral, and anti-inflammatory [268].	60 mL of decoction taken for two times a day for 14 days [267].

4	Adathodai Manapagu	Siddha	Antiviral activity [269].	10 mL twice a day [269].
5	Cydonia oblonga (Behidana), Zizyphus jujube (Unnab), Cordia myxa (Sapistan)	Unani	The immunomodulatory effect, antioxidant, anti-inflammatory, and antipyretic effect [269, 270 271].	Behidana - 3g Unnab - 5 Nos Sapistan - 9 Nos Boil these 3 contents in 250 mL water till half of its volume and filter it. Take this content two times a day for 14 Days [271].
6	Roghan Baboona	Unani	anti-inflammatory activity and analgesic activity [272].	As directed by the physician

- **Prevention against COVID-19 [273, 274]: -**

The best way to prevent the transmission of coronavirus is to restrict ourselves from the people having respiratory and coronavirus symptoms.

The other best thing that an individual can do is maintain proper hygiene, follow the basic guideline given by WHO and respective government health professionals, and, most importantly, practice social distancing (6 feet or 2 meter distance) to prevent viruses from transmission.

Tips for prevention from COVID-19 transmission: -

1. Take care of older people,
2. Wash hands for 20 seconds with soap and warm water,
3. Not to touch eyes with dirty hands,
4. Recommended gargling for 2 times a day with mouth wash containing chlorhexidine [275] or povidone-iodine gargle [275] or warm water containing salt and curcumin [273].

5. Not to go out if feeling sick or have any flu or cold-like symptoms,

6. If necessary, then only go out from home by covering the mouth and nose (3-ply mask or N95 mask or 3 layer cotton cloth), practice social distancing (at least 2-meter distance between two people), and always carry hand sanitizer (contain 90% ethanol or Iso-propyl alcohol).

7. Disinfects the objects or sanitize the purpose of frequently being used.

8. Use soap water to clean the utensils and dishware frequently used for cooking or eating.

9. Drink warm water throughout the day and practice meditation and pranayama for at least 30 minutes.

10. Use of turmeric, cumin, coriander, and garlic in cooking is beneficial.

11. Drink herbal tea or decoction made from Basil (Tulsi), Mint (Pudina), Carom seed (Ajwain), Launga (Clove), cinnamon stick (dalchini stick), Black pepper (Kali Mirch), Jaggary and dry ginger (shunthi) or add lemon juice for taste if needed.

12. Drink 'golden milk.' – Half tea-spoon turmeric powder in 150-200 mL hot milk for once or twice in the whole day.

13. Increase the intake of Vitamin-C Fruits in daily diet.

14. Take a giloy tablet or juice (Tinospora Cordifolia) two times a day as an immunity booster.

15. Have a sound sleep (at least 8 hours) and have a positive attitude towards life.

CONCLUSION:

The novel coronavirus or SARS CoV-2 is a life-threatening virus affected in more than 80 countries. More than 19 million humans are affected, and more than 0.7 million deaths occurred, considering a global threat by WHO. In the present situation, there is no specific drug or therapy available to cure this disease or not any single vaccine available to protect against novel coronavirus. As mentioned above, various features of this SARS-CoV-2 with their pathophysiology and mechanism of infection provide greater understanding to develop novel molecules, vaccines, and therapies to treat COVID-19.

The present article focuses on various possible treatments and prevention for COVID-19. Allopathy, Herbal, Siddha, Unani, and vaccine development are the safest way to protect the body against novel coronavirus. Some allopathic antivirals like remdesivir, favipiravir, etc. provide a better option as allopathic treatment for targeting the virus. Convalescent plasma Therapy has provided a new ray of hope for the treatment of COVID-19. Vaccines and novel drugs are also into a clinical testing period, which can offer a new way of saving lives and improve immunity against the novel coronavirus.

Herbaceous plants like giloy, ginger, ashwagandha, kalmegh, tulsi, ginger, turmeric, etc. have an immunostimulant effect that can provide immunity towards the novel coronavirus with minimal side effects. These plants also have an anti-inflammatory property and some amounts of antioxidants that help the body to repair damaged tissues. These plants also have a modulatory effect on various cytokines like IL-6, IL-12, and other inflammatory agents.

Siddha, Unani, and homeopathy provide a better way to prevent and develop a robust immune response against novel coronavirus.

Prevention is better than cure! It becomes the moral responsibility of every fellow to follow the guidelines issued by the WHO and the government authorities to stop the chain against transmission of this deadly virus.

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