A Review on Catastrophic Evolution of SARS-CoV to SARS-CoV2: A Global Pandemic

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Abstract: The coronaviruses, belonging to the family Coronaviridae, have caused a massive pandemic in December 2019 after their previous outbreaks as SARS-CoV and MERS. The outbreak is believed to have originated from the seafood and live market in the Hubei province of China. The Rhinolophus species are the natural hosts of this virus. This virus caused pneumonia and took away many lives before it was recognized as the novel Coronavirus. Very little information is available about the biology and nature of the novel Coronavirus. This article reviews multiple aspects encompassing its origin, epidemiology, pathogenesis, symptoms, and the global statistics of spread. Acute respiratory distress syndrome (ARDS) is the key symptom of this condition. Angiotensin-converting enzyme 2 (ACE2) helps in the penetration of the virus into the target cells. Deeper research and understanding are essential for the identification of antibodies that inhibit ACE2 and can prevent viral replication. Drug design and control of disease are crucial. In countries like India, where plant diversity is extensive, it is prudent to focus on plant-based alternative drugs. Many attempts have been made to review and curate the drug discovery attempts using immuno-informatic and bioinformatic tools.

Keywords: SARS-COVID-19, Acute Respiratory Distress Syndrome (ARDS), Rhinolophus species, ACE2 receptor, Orf 8 protein, natural drugs.

1. INTRODUCTION

Zoonotic viruses, and the diseases spread by them, have evolved with mankind over the centuries. Coronavirus (CoV), pseudo living RNA viruses, have the largest genomes of all RNA viruses [1]. Though they have evolved only 10,000 years ago, the molecular clock dating suggests that the most common ancestor of this existed around the same time. These viruses seem to have a diverse range of natural hosts. They are positive-sense RNA virus, classified under Nidovirales (Order), Coronaviridae (Family), Orphocoronavirinae (Subfamily), β-Coronavirus (Genera – α, β, γ, δ), and Sarbecovirus (Subgenera) (Fig. 1). Alpha and Beta coronaviruses are common in mammals, while gamma and delta coronaviruses use birds as their primary host [2]. Studies reveal that prior to mutations in 2002, virus native to civet cats mutated to spread as Severe Acute Respiratory Syndrome (SARS) and after a decade (2012), it infected camels and mutated to infect humans as Middle East Respiratory Syndrome (MERS). SARS-CoV and SARS-COV2 are classified under β-COVID genera that typically infect humans, bats, and wild animals. In the US, the first human to human transmission of SARS-COVID-19 was confirmed on 30th Jan 2020. The WHO named SARS-CoV2 as SARS-COVID-19 after a severe outbreak, classified COVID-19 (group 2B), the seventh member of CoVs (SARS-COVID-19) causing life-threatening unexplained pneumonia [3].

2. HISTORY OF CORONAVIRUS (CoV)

The first-ever human coronavirus was tracked by Tyrrell and Bynoe (1965), named B814 [4]. It was obtained from the tracheal organ cultures from the respiratory tract of an adult suffering from a common cold. In the late 1960s, Tyrrell with his group was working with the human strains and several animal viruses including bronchitis virus, mouse hepatitis virus, and, virus of swine. They were morphologically similar when viewed through an electron microscope. This group of viruses was later officially named as a coronavirus (CoV) and was accepted as a new genus [5]. According to a study [6], the seven CoVs are causative agents of human disease. The highly pathogenic SARS-CoV and MERS-CoV caused severe respiratory syndrome in humans. HCoV-NL63, HCoV-229E, HCoV-OC43, and HKV1 are human CoVs causing mild upper respiratory diseases. In December 2019, there was an outbreak of several pneumonia cases across China. Further investigations unraveled that it was caused by the 2019 - The novel Coronavirus, SARS-CoV2, and the latest SARS-CoV2 have an 80 % similar genome of SARS-CoV [7].
3. GLOBAL STATISTICS

3.1. Wuhan’s War on COVID-19

Wuhan is a metropolis, in Hubei, in central China. It houses about 11 million residents, 1.3 times that of New York (8.4 Million). This winter, the city was fighting against the novel coronavirus. This virus strain is believed to have originated from the seafood and live animal market in Wuhan, Huanan Seafood Market which was subsequently shut down on January 1, 2020. Figs. (2 and 3) [8-10] show a steep increase in the number of confirmed cases of COVID-19 and the reported increasing deaths. Based on the trends reported, The Center for Disease Dynamics, Economics and Policy (CDDEP) and John Hopkins University utilized INDIASIM software to predict the extent of the population to be affected by COVID-19 in the upcoming days using three scenarios in India, based on the data of several individuals quarantined and hospitalized. The categories are high (current lockdown, but insufficient social distancing), medium (moderate to full compliance of social distancing, but no change in the virulence of the virus), and low (optimistic with lowering virulence and other factors) as enlisted. It was observed in this prediction that a pool of cases is expected between 25th March 2020 and a peak on 25th April 2020 and a flattened curve after 25th July 2020 [11].

3.2. Epidemiology Outside China

On 30 January 2020, the World Health Organization declared the COVID-19 outbreak as the sixth Public Health Emergency of international concern (Fig. 4) [10]. South Korea has declared a war against COVID-19, with the total number of cases rising over 5,000, with Daegu a small town being the epicenter (Fig. 5) [11]. Japan has a completely different story. The total confirmed cases are reported to be 981, out of which 706 are the people who on-boarded the Diamond Princess Cruise ship. On February 3, a total of 10 people were tested positive for the epidemic virus. When the ship reached Yokohama, Japan, it was quarantined. By the time the ship was released, about 17% of the passengers were affected. On February 20, 2020, about 619 out of 3700 passengers were tested positive, with deaths reported (Fig. 6) [12] in Japan. Other countries with confirmed cases include Singapore, Hong Kong SAR, Thailand, Taiwan, Australia, Malaysia, Germany, Vietnam, the USA, Macao SAR, the UAE, Canada, France, the Philippines, the UK, Italy, India, Russia, Finland, Sweden, Sri Lanka, Cambodia, Nepal, Spain, and Belgium [13].

4. SYMPTOMS

Coronavirus (CoV) is one of the major pathogens that primarily targets the human respiratory system, gastrointestinal system, liver, and central nervous system. The novel SARS-CoV2 remains viable in aerosols for hours and on surfaces for days. The common symptoms of a SARS patient at the onset include fever (36°C), cough, fatigue, sputum production, headache, dyspnoea, leucopenia (2.91 × 10^9 cells/ L of blood), lymphopenia, and thrombopenia. The clinical symptoms, according to CT-chest, include pneumonia, RNAemia, Acute Respiratory Distress Syndrome (ARDS), Acute cardiac injury, and ground-glass opacity (subpleura of lungs) with inflammations. Unique symptoms, when the lower airway of the upper respiratory tract is targeted, include rhinorrhoa, sneezing, sore throat, upregulation of aspartate transaminase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase (LDH), C-reactive protein (CRP) (16.16 mg/L of blood) (Fig. 7) [14].

The latency period for COVID-19 is from 3-7 days on average, for up to 14 days, which is longer than SARS-CoV [15]. During this incubation period [16] people are highly contagious and can infect others on an average of 3.77 (2.23-4.82). Depending on the severity, COVID-19 is classified as mild, normal, severe, and critical cases, depending on the age...
Fig. (2). Global data of COVID19 - confirmed cases [8]. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Fig. (3). Global data on COVID-19 – deaths [9]. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Fig. (4). Global comparison of COVID-19 cases in February and March [10]. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*
and immune system. Reports have highlighted that the hospital staff was at higher risk of contracting the infection [17]. The majority of deaths have been reported in older patients (> 64 yrs) [18]. Accordingly, people who have not been exposed to SARS-CoV1 are all susceptible to COVID-19 disease. Reports of young adults confirm that they have been affected by chronic diseases (diabetes, hepatitis B) and patients as immuno-suppressants and with decreased immune function [19, 20].

5. PATHOGENESIS OF COVID-19

Pathogenesis of SARS-CoV was studied [21-23] and the pathogenesis includes blood level with high concentration of cytokines, chemokines (IL1-ß, IL1RA, IL7, IL8, IL9, IL10, BASIC FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIPα, MIPß, PDGFB, TNFα, and VEGFA) and promoting severity of the viral infection. Spike proteins (S) and nucleocapsid protein (N) confer viral stability. N protein is a structural protein functional in the efficiency of virion assembly and virus transcription [24]. The role of S protein is to mediate infection of target cells by binding to cellular receptors (ACE2) of sensitive cells and replication in cytoplasm. The sensitive cells to viral infection include lungs, immune organs, and systemic blood vessels [25]. This directs systemic vasculitis, decreased immune function [26] and extensive
pulmonary consolidation, diffuse alveolar damage, and the formation of the transparent membrane [27, 28] (Table 1).

| Characteristic          | Patient |
|-------------------------|---------|
| Age (years)             | 41      |
| Sex                     | Male    |
| Date of illness onset   | 20 December 2019 |
| Date of admission       | 26 December 2019 |

### Table 1. Clinical symptoms and patient’s data [28].

#### Signs and symptoms

|                          |         |
|--------------------------|---------|
| Fever                    | Yes     |
| Body temperature (Celsius)| 38.4   |
| Cough                    | Yes     |
| Sputum production        | Yes     |
| Dizzy                    | Yes     |
| Weakness                 | Yes     |
| Chest tightness          | Yes     |
| Dyspnœa                  | Yes     |
| Bacterial culture        | Negative|
| Glucocorticoid therapy  | Yes     |
| Antibiotic therapy       | Cefoselis|
| Antiviral therapy        | Oseltamivir|
| Oxygen therapy           | Mechanical ventilation |

6. ANIMAL RESERVOIRS FROM SARS-CoV TO SARS-CoV2 BY GENOMIC COMPARISON

The natural host of SARS-CoV is *Rhinolophus sinicus* (Chinese rufus horseshoe bat) (Figs. 8 and 9) was confirmed. Based on the studies [29], by genome sequencing, bats are the natural hosts for the earlier three CoVs. SARS-CoV2 shares 80 % of the gene sequence of SARS-CoV and confirms 96.2 % similarity of SARS-CoV2 with SARS isolated from *Rhinolophus affinis* (Figs. 10 and 11). Other intermediate hosts have been reported to be snakes and minks highlighting pangolins (Figs. 12 and 13) that share 99 % as intermediate hosts [30-32]. Homology analysis of mutated SARS-CoV shows ≥65 % identity and the query coverage of ≥95 % [33]. According to the genomic comparison (Fig. 14), the genome of SARS-CoV2 and SARS-CoV (Bat: SL-CoVZC45, MG772933) is 85 % similar to CoVZXC21, MG7722934. Thus, it confirmed that SARS-CoV2, CoVZC45, and VZXC21 have β-Coronavirus gene structure.
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Fig. (10). Distribution of *Rhinolophus affinis* in China. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Fig. (11). *Rhinolophus affinis* [35] (Intermediate horseshoe bat). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

**SYSTEMATIC POSITION**

| KINGDOM   | Animalia          |
| PHYLUM    | Chordata          |
| SUBPHYLUM | Vertebrata        |
| CLASS     | Mammalia          |
| ORDER     | Chiroptera        |
| FAMILY    | Rhinolophidae     |
| GENUS     | Rhinolophus       |
| SPECIES   | *Rhinolophus affinis* (Horsfield, 1823) [35] |

Fig. (12). Distribution of *Manis temminckii* in Africa. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Fig. (13). *Manis temminckii* [36] (Pangolin). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

**SYSTEMATIC POSITION**

| KINGDOM   | Animalia          |
| PHYLUM    | Chordata          |
| SUBPHYLUM | Vertebrata        |
| CLASS     | Mammalia          |
| ORDER     | Pholidota         |
| FAMILY    | Manidae           |
| GENUS     | Manis             |
| SPECIES   | *Manis temminckii* (Smuts, 1832) [36] |

ZPicture is an interactive Web-based sequence alignment and visualization tool for dynamically producing conservation profiles and identifying Evolutionarily Conserved Regions (ECRs). Zpicture analysis of genomic comparison of SARS-CoV2 AND SARS-CoV showed CoVs with high homology at the nucleotide level. It confirmed 6RD (Regions of Difference) in the genome sequence (Table 2). All the RDs provide new molecular markers and drugs.

7. INTERACTION BETWEEN COV S-PROTEIN AND HOST RECEPTOR ACE2 (ANGIOTENSIN-CONVERTING ENZYME2)

Genomic evidence proves a high degree of homology of the ACE2 receptor from animals (bats). ACE2 receptors were isolated from SARS-CoV-permissive Vero E6 cells *in vitro*. Sequence identities with SARS-CoV evince single intact ORF on gene 8 proving a bat origin CoVs [34-37]. A receptor binding motif (RBM) of spike protein (S) directly contacts ACE2 which facilitates CoVs to enter into the host system (respiratory-alveolar system). Reports of [38] suggest that ACE2 has specific key binding residues and functional receptors (SARS-CoV) and it also protects alveolar cells. Binding of spike protein (S) to ACE2 leads to alveolar injury during SARS [39]. Therefore down-regulation of ACE2 causes higher production of angiotensin II which increases pulmonary vascular permeability and correspondingly, stimulation of type 1A angiotensin II receptor (AGTR1A) leads to lung pathology [40]. Recent works showed that antibodies targeting ACE2 can block viral replication in Vero E6 cells *in vitro* [41].

8. PROTEOMIC COMPARISON

Studies using Blastp ensured that all encoded proteins of SARS-CoV2 are homologous to SARS-CoV [14]. Sequences
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Fig. (14). Genome organization of human coronaviruses (HCoVs) [37]. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 2. Regions of Difference (RD) with its gene in CoVs [29].

| Regions of Difference (RD) | No. of Nucleotides (nt) | Gene (Coding)                  |
|---------------------------|-------------------------|--------------------------------|
| RD1                       | 448 nt                  | Orf lab gene (Partial coding)  |
| RD2                       | 55 nt                   |                                |
| RD3                       | 278 nt                  |                                |
| RD4                       | 315 nt                  | S gene (Partial coding)        |
| RD5                       | 80 nt                   |                                |
| RD6                       | 24 nt                   | Orf 7b, Orf 8 genes (Coding)   |

showed 95-100 % homologous proteins, except for 2 (Orf 8 and Orf 10) in SARS-CoV2 having non-homologous proteins to that of SARS-CoV. Thus, differences in amino acid sequences in Orf 8 of SARS-CoV2 have sequences of conserved Orf 8 or Orf 8b derived from SARS-CoV [7]. Orf 8 protein (SARS-CoV2) does not have a known functional domain. In Orf 8b (SARS-CoV), there is an aggregation motif (VLVVL; 75-79 amino acids) that triggers intracellular stress pathways and activates NOD-like receptor family pyrin domain-containing-3 (NLRP3) inflammasomes. Nucleocapsid (N) protein (SARS-CoV2) has approximately 90 % amino acid identity (SARS-CoV) [43, 44]. Spike (S) proteins in stalk S2 in SARS-CoV2 are highly conserved and shares 99 % identity with two bat-SARS like CoVs (CoVZC45 and VZXC21). Spike proteins (S) of SARS-CoVs have 14 amino acid residues that are predicted to interact with the human ACE2 receptor for SARS-CoV. Accordingly [45, 46], eight amino acids are well conserved in the homology of SARS-CoV2 spike protein. Reports show demonstrated study on the receptor-binding domain of SARS-CoV2 was capable of binding the ACE2 receptor concerning SARS-CoV spike protein (Fig. 15) [31]. Thus, SARS-CoV2 strains use ACE2 receptors more effectively than SARS-CoV (2003) but less efficiently than human SARS-CoV (2002). Hence, the mutation of proteins showed a higher ability to infect and enhance pathogenicity than bat-like SARS-CoV, but lower pathogenicity than SARS-CoV [47, 48].

9. THERAPEUTICS AND TREATMENTS

9.1. Indian Plant-based Derivatives/Drugs as a Potential Cure Against Viral Infections

Plant medicine has been a promising remedy for curing many diseases in the past. Through the indigenous flow of knowledge, Siddha, Ayurveda, Unani, and Naturopathy have been ingrained in Indian traditional medicine. According to AYUSH (Ayurvedic, Yoga, and Naturopathy, Unani, Siddha, and Homeopathy), prevention of disease happens through lifestyle changes, proper diet, enhancing immunity, and remedies to prevent symptoms effectively [49]. According to their recommendations, the plants listed in Table 3 have been found to have an effective cure against this disease. Many plants have been observed to have prevented various illnesses, which can be effective in the case of coronaviruses due to their antiviral properties. Clinical trials are required for prescription [49, 50]. Table 3 shows that the following plants have been observed as immunopotents.
Fig. (15). Life cycle of COVID-19 [42]. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 3. List of plant species and their curative effect [50].

| Plant species & Homeopathy drug | Common Name / Sanskrit name | Effective against |
|--------------------------------|-----------------------------|-------------------|
| *Tinospora cordifolia*          | heart-leaved moonseed, guduchi, and giloy | Chronic fever |
| *Andrographis paniculata*       | creat or green chireta      | Fever and cold |
| *Cydonia oblonga*               | *Quince, amrutaphala*       | Antioxidant, immune-modulatory, anti-allergic, smooth muscle relaxant, anti-influenza activity |
| *Zizyphus jujube*               | Common jujube               | Antioxidant, immune-modulatory, anti-allergic, smooth muscle relaxant, anti-influenza activity |
| *Cordia myxa*                   | Sapistan plum               | Antioxidant, immune-modulatory, anti-allergic, smooth muscle relaxant, anti-influenza activity |
| Homeopathy drug - *Arsenicum album 30* | -                           | Effective against SARS-CoV-2, immune-modulator. |

Different researchers have evaluated the effects of the Indian plants on nCoV like, in *Bryonia alba* reducing lung inflammation, *Atropa belladonna*, and *Bignonia sempervirens* as effective against asthma and chronic lung diseases, and *Eupatorium perfoliatum* is found to be effective in treating major respiratory symptoms. But they require systematic exploration of how they can be utilized at the time of emergency [50]. In Human Influenza Virus – 1 Protease (HIV 1PR), inhibition mechanism is studied using *Acacia nilotica*, *Euphorbia granulate*, *Ocimum kilimadsharicum*, *O. sanctum*, *Solanum nigrum*, and *Vitex negundo* [51-54]. *Glycyrrhiza glabra* inhibits viral replication and modulates membrane fluidity in both HIV and SARS [55]. Some plants were examined for effects against SARS-CoV and
other similar viruses [56, 57]. *Allium sativum* was observed to have proteolytic, haemagglutination, and viral replication inhibition properties. *Andrographis paniculata* suppressed SARS CoV and HCoV kinds of viruses when targeted at NLRP3 and caspase – 1 [58, 59]. *Clerodendron spp* inactivated the viral ribosomes of SARS-CoV2 [60]. *Strobulanthus callosa* and *S. cusia* blocked HCoV- NL63 viral gene [61]. *Vitex trifolia* showed anti-mouse coronavirus activity (a surrogate of SARS-CoV) [62]. In the case of Coronavirus, plants that inhibit ACE are essential. Some plants were observed with this property like *Boerhavia diffusa*, *Punica granatum*, *Cynara scolymus*, and *Coriandrum sativum* [63-65].

Many studies were also focussed on the active compounds from natural plants and their effective properties were studied. The plants mentioned in Table 4 have been observed immunopotents. *Glycyrrhiza glabra*, also known as liquorice, according to [66], treats cold and cough due to the presence of the active compound glycyrrhizin. *Atropa belladonna* of the Solanaceae family contains atropine, as indicated by [67] is used to stop bronchial spasms along with many other properties of preventing motion sickness and as a pain killer. The garlic that we use in our daily food contains ajoene and diallyl thiosulfinate (allicin), which naturally strengthens our immune system. *Ziziphus spina-christi* having anti-HIV and anti tumor properties contains botulinic acid. [66]. *Andrographis paniculata* contains andrographolide and is effective for COVID-19 as it treats cough, cold, viral fever, and liver disorders. *Tinospora cordifolia*, commonly called amritballi-7 in India, contains Berberine [69], which is anti-diabetic, anti-allergic, anti-inflammatory, anti-pyretic, diuretic, and possesses immunomodulatory properties [67].

Developing countries particularly depend on traditional plants for health requirements [70]. 25% of the routinely used medicines constitute plant-derived compounds [69]. Molecular docking is one of the most important bioinformatics methods in drug designing. According to a study [66], viral inhibitors by natural compounds or drugs with minimal side effects were reported. In this work, a virtual library of phytochemicals that was reported in selected medicinal plants (Arabic area) was screened against protein targets of the COVID-19 virus (COVID: 3CL-protease structure) and compared with the proposed drugs (chloroquine and hydroxychloroquine).

Several docking studies were recently focussed on a safe and cost-effective attachment inhibitors, which are still required for the treatment of COVID-19 [70]. His works enhanced with anti-viral and molecular docking studies from Ayurveda, screened many natural products that can regulate and enhance the host immune system. It defends the host system against viral pathogen invasion and other coronaviruses in near future. Natural products/drugs such as nimbin, curcumin, withaferin A, pipereine, and nafamostat (known spike glycoprotein inhibitor) have a better binding affinity toward spike glycoprotein and its cellular receptor ACE2. The chemical structures and their properties of selected natural products were given in (Table 5) [70] and nimbin and curcumin have shown higher docking score and significantly nimbin revealed the highest binding efficiency with spike glycoproteins followed by curcumin. Other natural products also demonstrated better efficiency along with the studied synthetic drugs.

### 9.2. Chinese Plant- based Derivatives/ Drugs as Potential Cure against Viral Infections

In the Chinese province, herbal medicine has been practised widely to treat many infectious diseases even during nCoV outbreak. A study was conducted to record the frequency of the plants used in the different Chinese medicine formulae in the 23 provinces of China. Table 5 shows some of the common traditional formulae used as per the Huangdi’s Internal Classic, an ancient medical text of China [76]. Among the provinces of China, the Chinese medicine formulae were used for treatment. The formulae contained about 54 different herbs, where 19 herbs had a frequency of more than 3 in the COVID-19 preventive formulae which were used as treatment for the general population. Among them, *Radix astragali* and *Glycyrrhizae Radix Et Rhizoma* had the highest frequency [71].

### Table 4. Active compounds isolated and their effective properties [70].

| Common name       | Compound active          | Effective properties                                                                 |
|-------------------|--------------------------|-------------------------------------------------------------------------------------|
| Liquorice         | Glycyrrhizin             | treats cold and cough                                                                |
| Belladonna        | Atropine                 | stops bronchial spasms in asthma and whooping cough, treats cold and hay fever, prevents inflammatory bowel disease, motion sickness, and is a pain killer. |
| Garlic            | Ajoene                   | Strengthens immune system                                                            |
|                   | diallyl thiosulfinate (allicin) |                                                                                     |
| Christ's thorn jujube | Betulinic acid            | anti-HIV and antitumor activity                                                      |
| Green chireta     | Andrographolide          | treats cough, cold, viral fever and liver disorders                                  |
| Amritaballi -7    | Berberine                | anti-diabetic, anti-allergic, anti-inflammatory, anti-pyretic, diuretic and immunomodulatory properties |
Table 5. List of natural products evaluated for *in silico* antiviral activity against SARS-CoV-2 [70].

| Ligand            | Source (Common/ Sanskrit name) | Pharmacological functions                                      |
|-------------------|--------------------------------|----------------------------------------------------------------|
| Hydroxychloroquine | Synthetic drug                 | Antimalarial agent, Treatment of COVID-19                      |
| Nafamostat        | Synthetic drug                 | Antiviral agent                                                |
| Captopril         | Synthetic drug                 | Antihypertensive agent                                         |
| Nimbin            | *Azadirachta indica* (Neem/Nimbka) | Antinflammatory, antimicrobial                                  |
| Curcumin          | *Curcuma longa* (Turmeric/ Haridra) | Antinflammatory                                                 |
| Withaferin A      | *Withania somnifera* (Indian ginseng/ Ashwagandha) | Immunomodulator, antiangiogenic, antitumor agent                |
| Piperine          | *Piper nigrum* (Black pepper/ Maricha) | Antimicrobial, immunomodulator, hepatoprotective, antioxidant  |
| Mangiferin        | *Mangifera indica* (Mango/ Aamra) | Antiviral, andanthelmintic, antinflammatory, analgesic          |
| Thebaine          | *Papaver somniferum* (Poppy/ Khas-khas) | Analgesic, antitussive                                         |
| Berberine         | *Berberis vulgaris* (Barberry/ Daruharidra) | Antidiabetic, antihypertensive, antinflammatory, antitussive   |
| Andrographolide    | *Andrographis paniculata* (Green chireta/ Kalamegha) | Antiviral, antiinflammatory, antineoplastic                     |
| Quercetin         | *Citrus aurantium* (Bitter orange/ Naranga) | Antioxidant, neuroprotective, antiviral, anticancer, antimicrobial, anti-inflammatory |
| Luteolin          | *Capsicum annuum* (Bell peppers/ Mahamarichika) | Antiiinflammatory, antioxidant, anticancer, antitussive, antitussive, anti-inflammatory |
| Resveratrol       | *Vaccinium angustifolium* (Blueberry/ Nila badari) | Antiinflammatory, antioxidative                                 |
| Naringenin        | *Citrus paradisi* (Grapefruit/ Madhukarkati) | Antiinflammatory, antioxidative, antidyssipidemic, antiobesity, anti diabetic, antifibrotic, |
| Zingiberene       | *Zingiber officinale* (Ginger/ Singabera) | Antiinflammatory                                                |
| β-Caryophyline    | *Syzygium aromaticum* (Clove/ Devakusuma) | Antiinflammatory                                                |
| Citronellol       | *Rosa damascena* (Damask rose/ Satapatri) | Antiinflammatory, antibacterial, antifungal                     |
| Eugenol           | *Ocimum sanctum* (Holy basil/ Tului) | Antioxidant, neuroprotective, antiviral, anticancer, antimicrobial, anti inflammatory |
| Gallic acid       | *Emblica officinalis* (Indian gooseberry/ Amalaki) | Antibacterial, antifungal, antiviral, anti inflammatory, antihypertensive, antioxidant, antitussive, antidiabetic |
Three studies were conducted during the SARS epidemic. A controlled study was designed to evaluate an herbal formula for SARS in the Hong Kong province [72, 73]. The sample size comprises 16,437 individuals with 1063 members consuming herbal medicine and 15374 consuming non-herbal medicine. It was observed in the results that those who opted for herbal medicine did not get infected by SARS, whereas, in the patients who took non-herbal medicines, 64 out of 15347 were infected with SARS. 19 patients suffered minor adverse effects after the herbal medicine like sore throat and dizziness [72, 73]. Two single cohort studies were conducted in Beijing, China with a sample size of 3561 and 163 respectively. In one study conducted by Xu et al., only first-line medical staff were considered and the course of study was 6 days [79] and 12 - 25 days respectively [80].

### Table 6. Ingredients of herbal formulae and study period for preventing SARS.

| Latin name | Scientific name | Pinyin | Duration of study |
|------------|----------------|--------|------------------|
| Folium mori | Morus alba | Sangye | 14 days [78] |
| Flos chrysanthemi | Chrysanthemum indicum | Juhua | |
| Semen armeniacaeammarum | Prunus armeniaca | Xingren | |
| Fructus forsythia | Forsythia suspensa | Lianqiao | |
| Herbamertae | Mentha arvensis L. | Bohe | |
| Radix platycodonis | Glycyrrhiz auralensis | Jiegeng | |
| Radix glycyrrhizae | Glycyrrhiz auralensis | Gancao | |
| Rhizomaphragmitis | Phragmiteskarka | Lugan | |
| Radix astragali | Astragalus membranaceus | Huangqi | |
| Radix saposhnikoviae | Divaricate saposhnikovia | Fangfeng | |
| LoniceraeJaponicae Flos | Lonicera japonica | Jinyinhua | 6 days [79] |
| Radix astragali | Astragalus membranaceus | Huangqi | |
| RhizomaAtractyloidisMacrocephalae | AtractylodesmacrocephalaKoidz | Baizhu | |
| Radix saposhnikoviae | Divaricate saposhnikovia | Fangfeng | |
| Glehniae Radix | Radix glehniae | Shashen | |
| Crystal sugar | | Bingtang | |
| Radix astragali | Astragalus membranaceus | Huangqi | 12 – 25 days [80] |
| RhizomaAtractyloidisMacrocephalae | AtractylodesmacrocephalaKoidz | Baizhu | |
| Radix saposhnikoviae | Divaricate saposhnikovia | Fangfeng | |
| Cyrtomium fortune J. Sm. | Cyrtomium fortunei | Guanzhong | |
| Isatidis Folium | Isatis tinctoria | Daqingye | |
| Radix Scutellariae | Scutellaria baicalensis | Huangqin | |
| Talcum | | Huashi | |
| Radix glycyrrhizae | Glycyrrhiz auralensis | Gancao | |

The formula adopted was Yupingfeng powder consisting *Radix astragali* (RA), *Rhizoma atractyloidis* (RAM) and *Radix saposhnikoviae* (RS) (weight ratio 2:2:1) plus coupled with heat-clearing and detoxifying herbs [74]. The results showed that the participants who received herbal medicine did not get infected by SARS.

### 9.3. The Potential Clinical uses of Dexamethasone

Dexamethasone is a corticosteroid hormone used to treat allergic reactions, arthritis, blood/hormone/immune system disorders, certain skin and eye condition, breathing problems, bowel disorders, and certain cancer. It is employed as a diagnostic tool for Cushing’s syndrome, an adrenal gland disorder. Studies suggest that they can slow down the bone
9.3.1. Role of Dexamethasone in the Randomized Treatment of Coronavirus Outbreak

Dexamethasone is among the most affordable drugs used for the treatment of COVID-19. A randomized, controlled trial was conducted in the United Kingdom. For those patients in ventilator support, the death rate was reduced [85]. A total of 2104 patients were randomized to receive dexamethasone with a dose of 6mg/day either by intravenous injection or by mouth for ten days and were compared with 4321 patients who took usual hospital care. Among the patients who received usual hospital care, 28-day mortality was highest observed in those who required ventilator support (41 %); intermediate, in patients requiring only oxygen treatment (25 %), and the lowest observed in patients who required no respiratory intervention (13 %). Significantly, it reduced deaths by one-third in patients taking ventilator support and by one-fifth in patients receiving oxygen only.

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**Table 7. List of plants from the Chinese medicine used for the treatment of nCoV disease [71-74].**

| Name of the plant | Common Name (Chinese name) | Properties and Usage frequency in Chinese medicine formulae |
|------------------|---------------------------|-------------------------------------------------------------|
| *Radix astragali* | Huangqi                   | Strengthen the immune system and reduce inflammation; 16    |
| *Radix glycyrrhiza* | Gancao                   | Fundamental herbs used in traditional Chinese medicine; 16  |
| *Radix saposhnikoviae* | Fangfeng                | 13                                                          |
| *Rhizoma atractyloides macrocephala* | Baizhu               | Tonifying and invigorating the spleen; 12                   |
| *Lonicerae japonicae flos* | Jinyinhua                | Anti inflammatory, antitumor, antioxidant, anti-allergy, immunomodulating and anti-bacterial activities; 12 |
| *Fructus forsythia* | Lianqiao                 | Inhibition on influenza virus, leptospira, and other pathogen. It has also anti-inflammatory and anti-pyretic effects; 9 |
| *Atractylodis rhizoma* | Cangzhu                 | 8                                                           |
| *Radix platycodonis* | Jiegeng                  | 8                                                           |
| *Pogostemonis herba* | Huoxiang                | 7                                                           |
| *Cyrtomium fortune J. Sm.* | Guanzhong               | 7                                                           |
| *Perillae folium* | Zisuye                   | 6                                                           |
| *Rhizoma phragmites* | Lugen                    | 5                                                           |
| *Glehniae radix* | Shashen                   | 5                                                           |
| *CitriReticulatae pericarpium* | Chenpi                | 5                                                           |
| *Ophiopogonis radix* | Maidong                  | 5                                                           |
| *Eupatorii herba* | Peilan                    | 4                                                           |
| *Folium isatidis* | Banlangen                 | 3                                                           |
| *Coicis semen* | Yiyiiren                  | 3                                                           |
| *Folium mori* | Sangye                     | 3                                                           |
| *Radix astragali* | Huangqi                   | 16                                                          |
| *Glycyrrhizae Radix Et Rhizoma* | Gancao              | 16                                                          |
| *Radix saposhnikoviae* | Fangfeng                | 13                                                          |

Erosion by reducing inflammation of the joints, which is potential in the treatment of arthritis [82]. It is reported to have immune-modulatory effects on cytokines in-vitro. When they were examined through peripheral blood mononuclear cells, followed by mitogenic stimulation at the level of secreted product and mRNA production, it was observed that dexamethasone inhibited markedly the expression of all the cytokines that were tested (IL-2, IL-4, IL-6, IL-10, IFN-γ, and TNF-α) based on a dose-dependent fashion [83]. Another study was conducted to study the efficacy of topical dexamethasone in the treatment of allergic inflammation in the conjunctiva, using a mouse experimental model. It was observed that it was efficacious in suppressing eosinophil and lymphocyte infiltration in subconjunctival tissue in the mouse model. However, IgE productive mechanisms seemed to influence the productive Cε gene expression in the conjunctiva tissue [84].
Based on these studies, we can observe that one death could be prevented by the treatment of eight ventilated patients or 25 patients who took oxygen alone [86]. Another study reported that corticosteroid therapy consisting of methylprednisolone, dexamethasone, and hydrocortisone was beneficial in treating SARS-CoV patients [87]. Other pieces of evidence show that patients who had ARDS, and were not infected with COVID-19 had reduced consequences when dexamethasone was taken in low doses for ten days [88].

10. PROPHYLACTIC MEASURES

To decrease the rate of new COVID-19 cases and to control the infection, several steps are being taken worldwide. Countries have been high on alert on the assessment of the travelers arriving from mainland China; treating the infected person in quarantine centers. Above all these governmental measures, one should watch out for the virus by cleaning hands frequently, avoiding close contact with the affected individuals, and cooking the food properly before consuming it. People with the acute respiratory syndrome should habitually wear a mask, maintain a certain distance, and cover their mouth with a mask or disposable tissues while sneezing or coughing and then washing hands immediately. Any symptoms recognized should be treated, and one should seek immediate health care service (Fig. 16).

According to the WHO [89], when a case is identified in a community based on observable symptoms, the person is advised to be quarantined for 14 days. Based on the development of further symptoms, actions are initiated to trace their contacts and quarantine them. The suspected patients are tested for the presence of the virus either by Real time-PCR (RT-PCR) or by serological techniques. For RT-PCR, the sputum, lavage, and aspirate are collected from the lower respiratory tract; nasopharyngeal swabs, wash, and aspirate for upper respiratory tract are collected. Personnel protective equipment is essential during sample collections for viral diseases. If the test results are negative for two times of testing in periodic intervals, the person can be let free from quarantine. If positive, continue with medical support.

An outbreak assessment is essential to analyze the spread of diseases (Fig. 17) [48]. For the containment of spread in a community, enhanced surveillance is essential. Investigations must work with the objectives of rapid detections to prevent widespread infection through human to human transmission. Knowledge objectives ensure the key epidemiological, clinical, and virological characteristics of the reported cases which also determines the efficiency of the transmission from human to human in a community. Risk communication remains a key aspect during an outbreak in a community. This can be achieved using the media, public statements, and engagement with communities. Preventing the spread of undesirable news is another key aspect of overcoming unnecessary fear. The Government should provide accurate knowledge and clarify if any misinformation is spread in order to help their country combat the epidemic disease.

11. UNRESOLVED ISSUES

On March 5, there were about 80,409 infections and 3,012 deaths in China. Daily infection and death rates decreased in China. On March 5, the number of new cases dropped down to 139 out of which 134 were those of Hubei. The recovered patients are claimed to be 52,000. However, the recovered patients were tested positive even after they
were discharged. Health experts suggest that they were unlikely to be infected a second time, more likely the tests were improper or that the patient was undergoing a long course of the disease. On April 21, 2020, there were about 751,273 infections and 35,884 deaths reported in the United States of America, which is the highest recorded so far. In Italy, 2,00,210 cases have been recorded with 20,852 deaths reported so far. In India, 18,601 cases have been recorded with 590 deaths so far [90]. The presence of SARS-CoV2 in stools was also observed. Whether it can be transmitted through the faecal-oral route is still unclear. It is believed that coronaviruses would survive on environmental surfaces and other inanimate objects; but the novel coronavirus is not detected in the environment. The current situation also points out that the efficacy of the disinfectants is lacking [91].

![Diagram](https://example.com/diagram.png)

**Fig. (17).** Types of outbreak assessments to be performed [48]. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

12. FUTURE DIRECTIONS TO CONTROL THE SPREAD OF COVID19

Accordingly, the people of Wuhan in an epidemic situation (54,000 confirmed patients) in Hubei province, China were lacking effective antiviral drugs, and the prognosis of patients depended on age and physical condition [92, 93].

i. To ensure methods to reduce person-to-person transmission by effective guidelines is necessary.

ii. The number of dead exceeded with clinically recovered and the mutation of SARS-CoV2 is making vaccine development, a challenging task. The necessity of more sensitive inspection methods and effective drugs is essential.

iii. Usage of decontaminating agents (disinfectants) is necessary and alternative transmission route like wet and contaminated objects is to be focussed.

iv. Travel screenings to control spread and public health measures need to be implemented.

v. Epidemiological changes like transmission routes, subclinical injections, adaptation, and evolution, spreading from reservoirs to humans through intermediate hosts, need to be focussed.

vi. Positively tested patients with no clinical symptoms need to be considered.

vii. To investigate the highly contagious behavior of COVID-19 than SARS.

viii. The spread of viral infection is by droplets or close contacts. But aerosol and faecal-oral transmission still need to be studied.

The possibilities are:

i. The clinical course of SARS and MERS was highly similar; the two may have similar pathogenesis. Antiviral therapies can be implemented by relating SARS-CoV, SARS-CoV2 and MERS-CoV [94].

ii. Since 80% of the genome of SARS-CoV2 are similar to SARS-CoV, clinical drugs, and therapies for treating SARS may be used as a reference for COVID-19 treatment [93].

iii. A study conducted to relate humidity and temperature in the transmission of SARS-CoV2 showed beneficial results. It is expected that relatively high temperatures and humidity can lower the transmission of SARS-CoV2 [95].

iv. Spike in stalk S2 in SARS-CoV2 is highly conserved and shares 99% identity with two bat-SARS like CoVs (CoVZC45 and VZXC21). Therefore, antiviral peptides against S2 have the potential to be effective treatment [96].

v. Another study was conducted using immune-informatics to map the globally conserved nonamer epitopes in the SARS-CoV2 genome. This will help to generate a potent immune response. The sequences bearing these nonamer epitopes were MGYINVFAPFTYISLLLC and KVSIWNLDYINLI across proteins and alleles [97].

vi. Antibodies against N-proteins of SARS-CoV are approximately 90% amino acid sequences identical to N-proteins of SARS-CoV2. Therefore, serum-based assay will provide an effective result [44].

vii. RDs of SARS-CoV with CoV2 provide new molecular markers for the identification and development of new drugs against CoV2; and to analyze the biological functions of Orf8 and Orf10 proteins in SARS-CoV [14].

viii. Convalescent plasma therapy is yet another attempt by drawing the serum from coronavirus disease recovered patient and is given to critical SARS-CoV2 patients. The procedure is an attempt to transfer immunity through the plasma to recover from the disease. Indian Council of Medical Research (ICMR) has currently obtained permission and the procedure is under clinical trial [98].

CONCLUSION

The outbreak of the SARS-CoV2 has left mankind struck. A potential cure is the need of the hour, which is still in the development phase. This can happen effectively only if the genetic makeup of the virus is completely analyzed. It is also an alarm for mankind about the ability of viruses to mutate and spill over to occur. This pandemic outbreak serves as an evident example of Darwin’s theory of natural selection which says “Survival of the fittest”. The population encompassing a weaker immunity is prone to infection and
requires preventive measures like quarantine. A combination of drugs can suppress the symptoms but not treat the underlying virus. The various attempts of drug development using computational tools are a ray of hope for the development of a drug for the population. Many studies have also been highlighted out using plant sources that are supportive of a diverse country like India. India is very focussed on COVID vaccine projects monitored by ICMR and recent attempts were accomplished in developing Covaxin, the first indigenous vaccine being developed by the former in collaboration with Bharath Biotech and expecting its clinical trials in August 2020.

In the Indian scenario, the climate and complete lockdown at different phases are minimizing the curve as it was observed during the previous outbreaks in various parts of the world.

**LIST OF ABBREVIATIONS**

| Abbreviation | Description |
|--------------|-------------|
| HCoV         | Human Coronavirus |
| RNA          | RiboNucleic Acid |
| SARS         | Severe Acute Respiratory Syndrome |
| MERS         | Middle East Respiratory Syndrome |
| ARDS         | Acute respiratory distress syndrome |
| ACE2         | Angiotensin converting enzyme 2 |
| α, β, γ, δ CoVs | Alpha, Beta, Gamma and Delta coronaviruses |
| CDDEP        | Center for Disease Dynamics, Economics and Policy |
| AST          | ASpartate Transaminase |
| ALT          | ALanine amino Transferase (ALT), |
| LDH          | Lactic DeHydrogenase (LDH), |
| CRP          | C-reactive protein |
| IL           | InterLeukin |
| IL1RA        | InterLeukin-1 Receptor Antagonist |
| FGF2         | Fibroblast Growth Factor 2 |
| G-CSF        | Granulocyte-Colony Stimulating Factor |
| GMCSF        | Granulocyte-Macrophage Colony-Stimulating Factor |
| IFNγ         | Interferon Gamma |
| IP10         | Inducible Protein 10 |
| MCP1         | Monocyte Chemoattractant Protein 1 |
| MIP          | Macrophage Inflammatory Proteins |
| PDGFB        | Platelet Derived Growth Factor subunit B |
| TNFα         | Tumor Necrosis Factor Alpha |
| VEGFA        | Vascular Endothelial Growth Factor A |
| S            | Spike protein |
| N            | Nucleocapsid protein (N) |
| ECRs         | Evolutionarily Conserved Regions |
| RD           | Regions of Difference |
| RBM          | Receptor Binding Motif |
| AGTR1A       | Type 1A Angiotensin II Receptor |
| Vero E6 cells | Vero lineage Epithelial cells |
| Orf (8, 10)  | Open Reading Frame (8, 10) |
| NLRS/NOD-Like Receptors | Nucleotide-Binding Oligomerization Domain-Like Receptors |
| AYUSH        | (Ayurvedic, Yoga and Naturopathy, Unani, Siddha and Homeopathy) |
| HIV 1PR      | Human Influenza Virus-1 Protease |
| NLRP3        | NOD-, LRR- and Pyrin Domain-Containing Protein 3 |
| RT–PCR       | Real time-Polymerase Chain Reaction (RT-PCR) |
| ICMR         | Indian Council of Medical Research |

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