

COVID -19: Etiology, Transmission, Epidemiology, Treatment and Clinical trials

Abstract

In 2019, human race again came across a highly transmittable and pathogenic viral infection viz. COVID-19 and along with its pandemic nature, caused severe acute respiratory syndrome (SARS), and owes its emergence from the local seafood market of Wuhan city, China. Corona virus is currently prevalent all over the world wherein it caused infection in more than 2959929 individuals worldwide with mortality rate nearby 6.84% in approximately 213 countries within a short span of time and the infection due to this virus is still on a higher verge. The data showed that the transmission rate of COVID-19 is higher than the previous viral infections, particularly because of changes in genetic recombination at S protein in the RBD region. Till now there is no approved treatment available against COVID-19 infection and has been observed for human to human transfer widely. The present review summarizes the etiology, transmission, epidemiology, possible approaches for the treatment of COVID 19 and Clinical trials.

Key words: Severe acute respiratory syndrome coronavirus (SARS), COVID-19, Etiology, Transmission, Epidemiology, Treatment and Clinical trials

Introduction

Now a day's human race is facing a life threatening new pandemic disease caused by COVID-19, which started from Wuhan city, China, and on December 31, 2019 first case was reported to World Health Organization (WHO) office in China, with unexplained low respiratory tract infections. At that context of time, nobody knew about the causative agent and scientists classified it as "pneumonia of unknown etiology". Later, after the intensive

outbreak investigation program, Chinese Center for Disease Control and Prevention (CDC), reported a novel virus belonging to coronavirus (CoV) family [1]. In the beginning, the virus was named by the scientists as 2019-nCoV and later on International Committee on Taxonomy of Viruses (ICTV) coined it as SARS-CoV-2 virus because its symptoms being very similar to SARS, but on February 11, 2020, WHO Director, announced this new CoV as "COVID-19" (acronym of "coronavirus disease 2019). On February 26, 2020, first case of COVID-19 was reported in United States, and it was reported that this infection was highly contagious and spreads quickly via human-to-human transmission. The cases due to COVID-19 soon became prevalent wherein involving around 12 countries with more than 8560 cases and approximately 860 deaths globally. As per the International Health Regulations (IHR) 2005, WHO declared it as a global Health Emergency of International Concern (PHEIC) in order to alert all countries regarding COVID-19 on January 30, 2020. Till March 11, the number of COVID-19 patients outside the China has increased with more than 1,16,000 cases and over 3500 deaths in around 112 countries and thus COVID-19 disease was declared as global pandemic by WHO.

As per the Literature, it is evident that earlier human population have also faced such serious viral epidemic situation in last two decades with H1N1 influenza in 2009, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and recently in 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia [2]. Both MERS and SARS cause illness from normal common cold to severe respiratory disorders, and both owe their origination from bats with initial transmission to Himalayan palm civet (SARS-CoV) and camel (MERS-CoV) and later jumps with transmission in to human race but unfortunately still the source of origin and mode of transmission of COVID-19, is yet to be explained.

Worldwide researchers are working tirelessly to get a right prevention and therapeutic strategies against COVID-19 in order to protect the human race. However till date,

information has been gathered from the two-way communication network named Information Network for Epidemics (EPI-WIN) developed by WHO regarding transmission mechanisms and clinical spectrum, that is emphasizing the fact that social distancing and isolation are the best weapons for reducing the viral transmission among the community in the present context of time along with the simple measures of maintaining proper hygiene and sanitization methods.

Etiology

The word coronavirus has been derived from the Latin word *coronam* means crown, which is single strand RNA virus, around 65–125 nm in diameter, crown-like microscopic appearance as shown in Figure 1. Additionally, CoVs viruses belongs to *Coronaviridae* family, order *Nidovirales* with subfamily *Orthocoronavirinae* that further subdivides into 4 genera's namely Alpha, Beta, Delta and Gamma-coronavirus (CoV). Generally almost all viral infections caused hepatic, respiratory and neurological disorders in animal's species. First HCoVs infection in humans was identified in 1960. After the genomic study of Wuhan patients suffering with pneumonia, researchers confirmed that this novel virus belongs to beta group of coronavirus and has 89% nucleotide similarity with bat SARS-like-CoVZXC21 and around 82% nucleotide similarity with human SARS-CoV, having single-stranded RNA with 29891 nucleotides encoding around 9860 amino acids [2].

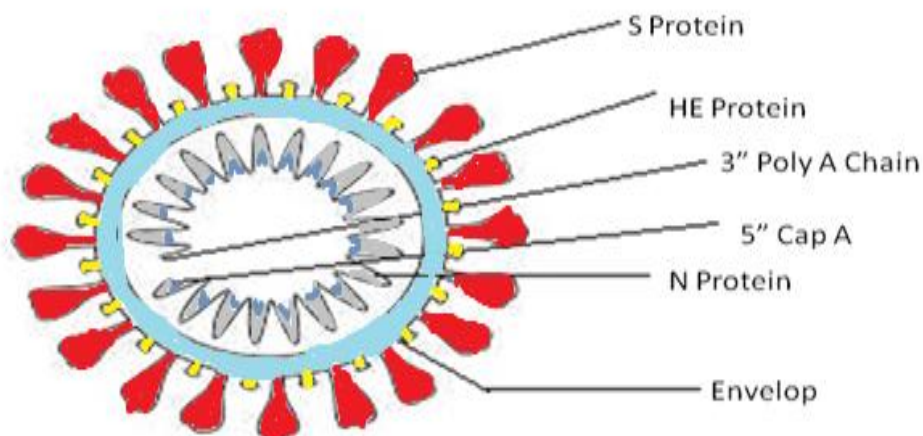


Figure 1: COVID-19 structure

Transmission

Earlier it was presumed that COVID-19 transmission occurred via animal to human exposure like SARS virus as shown in Figure 2, but later on researchers observed that subsequent cases were not associated with such exposure and concluded that it could be transmitted from human to human also. As per the data obtained from China CDC and local CDCs it is believed that COVID-19 transmission also occurred like other viral infections like by respiratory droplets, close contact with infected person or indirect contact with surfaces or objects used by infected person. **However based on the available data there is no evidence which confirms that the virus is isolated in faeces and cause GI infections.** As per the available literature, the reported incubation time of COVID-19 is 3 to 7 days on an average with longest duration of 12.5 days. With the current statistics, it is also evident that each infected person can transmit the infection to 2.2 individuals [3]. Keeping in mind the above statistics and information received from the initial reports, many studies by different countries are in process to better understand the underlying mechanisms, mode of transmissions, incubation times, and duration of COVID-19.

SARS Virus CoV 2 Transmission

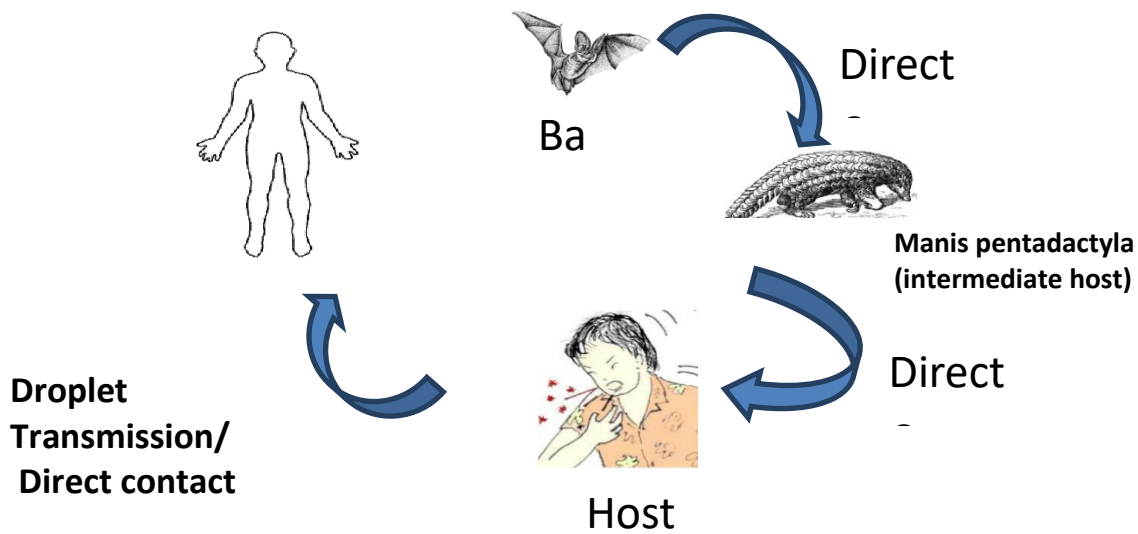


Figure 2: Transmission cycle of SARS virus

Epidemiology

As per the prevalence data provided by the WHO Information Network for Epidemics (EPI-WIN) dashboard related to COVID-19 infection, it is evident that there are around 2959929 confirmed cases, 73278 new cases and 202733 deaths have been recorded worldwide from the beginning of the pandemic till April, 2020. The countries of most cases are United States (976403), Spain (226629), Italy (197675), France (162100), Germany (157120), United Kingdom (152840), Turkey (110130), and Iran (90481) as shown Figure 3. This epidemiological scenario is varying on day to day basis with the following sources providing most trustable and correct information:

1. Information Network for Epidemics (EPI-WIN) dashboard;
(https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200330-sitrep-70-covid-19.pdf?sfvrsn=7e0fe3f8_2)
2. The Johns Hopkins Center for Systems Science and Engineering site;
(<https://coronavirus.jhu.edu/map.html>)

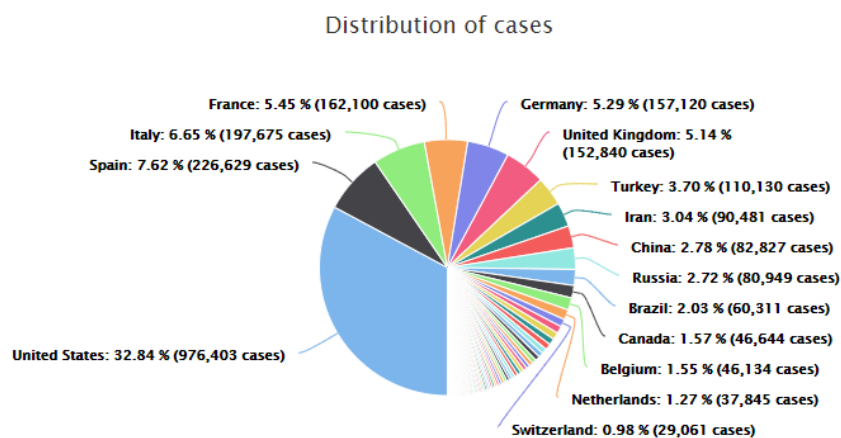
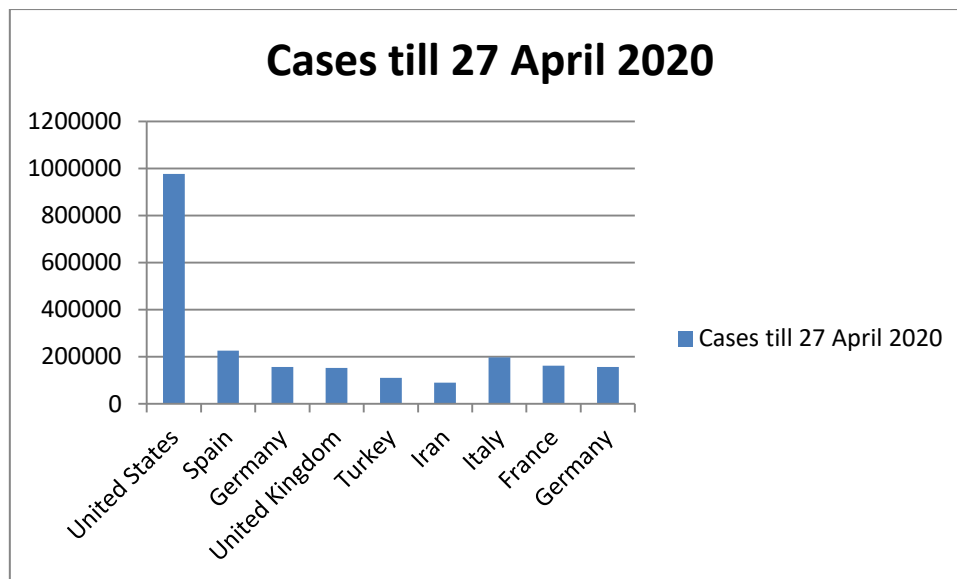


Figure 3: Chart of the countries having most cases globally till 27 April 2020

Reference: <https://www.worldometers.info/coronavirus/worldwide-graphs/#countries-cases>

Prevention

As per the available data received from various literature and health organizations, all scientists recommend that the preventive measures as shown in figure 4 would be very useful to limit the spread of COVID-19 cases. Current strategies are focused on (a) isolation of patients (b) social distancing (c) use appropriate measures during the diagnosis and (d) the provision of clinical care to an infected patient along with maintaining proper hygiene and adopting sanitization methods.

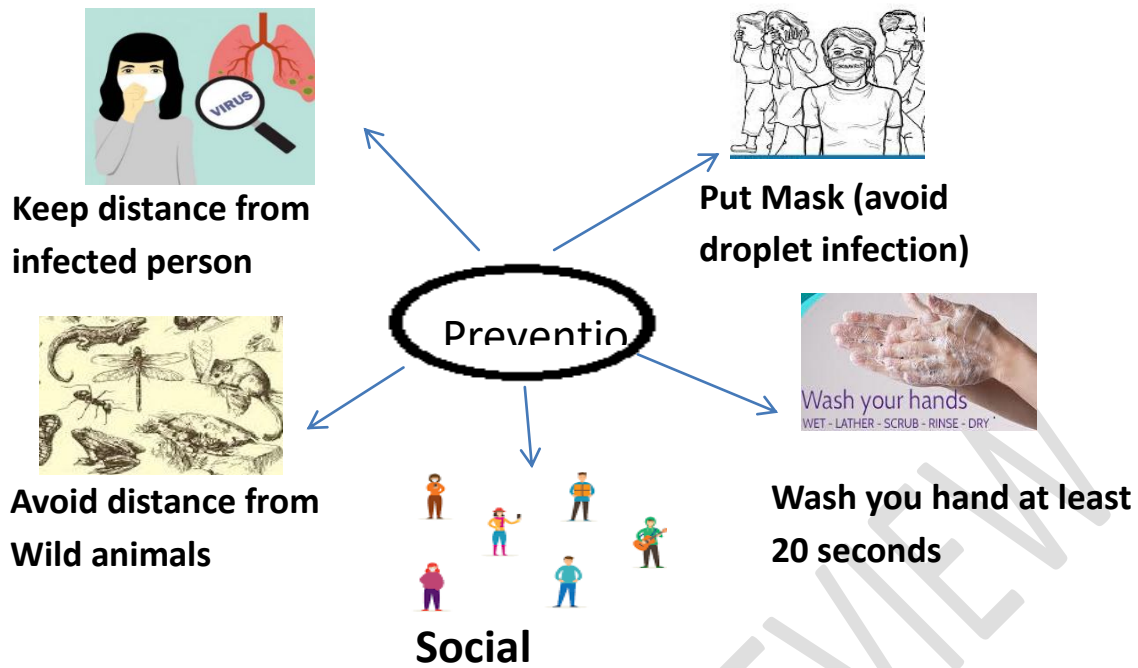


Figure 4: Preventive measures should be taken to avoid spreading of COVID 19

Possible treatment approaches for the viral outbreak

In order to understand the exact mechanisms of the COVID-19 outbreak, more understandings have to be done to find out the source of origin and transmission of the virus. However it is initially believed by the researchers that raccoon dogs [4] and palm civets may be the key reservoirs, but data obtained from samples isolated from the Wuhan market showed more than 80% genome of novel COVID-19 is similar to human SARS-like bat CoV and suggesting that the bat might be the key host. To understand the underlying mechanism, transmission and developing new therapeutic strategies to eradicate the COVID 19 infection, suitable animal model would play an important role. From the historic times, animal models have been a main stake and utilized for understanding of SARS-CoV infection in particular the pathogenicity of SARS-CoV-2, because of more than 80% genome similarity observed for COVID-19 and human SARS-like bat CoV. Unfortunately till date, no approved therapeutic treatment is available to treat COVID-19 globally, but some broad-spectrum antibiotics and anti-viral drugs are being used to reduce the severity of the infection. There

are three different approaches nowadays used by the clinicians of different countries for the treatment of the COVID 19 i.e. repurposed drugs, antibodies and vaccines.

1) **Repurposed drugs:** These drugs are the existing first line of defence in today's situation. These are basically the antiviral drugs used in the treatment of MERS and SARS and the immunomodulators.

a) **Antiviral Drugs:** These drugs are used to inhibit the genetic material synthesis of the virus and hence there will be no replication of the viral genome. Favipiravir is the drug which was approved for the treatment of Influenza. Japanese group has tested it in on 340 Covid-19 patients and found that it is a safe and effective treatment [5]. This drug is effective in mild to moderate infection but it is unclear that how effective it is in the severe cases. However the Japanese government has not approved it for the large scale use. Remdesivir combination with chloroquine blocked the SARSCoV-2 replication and have shown promising impact on the patients who have clinically recovered. Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature terminat other anti-viral drugs such as Nafamostat, Ritonavir, Nitazoxanide, Baricitinib, Ribavirin, Penciclovir etc are currently being evaluated against COVID-19 [6]. Our preliminary data showed that remdesivir also inhibited virus infection efficiently in a human cell line (human liver cancer Huh-7 cells), which is sensitive to 2019-nCoV [7]. However other anti-viral drugs such as Nafamostat, Ritonavir, Nitazoxanide, Baricitinib, Ribavirin, Penciclovir etc are currently being evaluated against COVID-19 [8].

b) **Immunomodulators:** The corona virus overstimulates the immune system; therefore auto-immunomodulators can be used for the treatment of the COVID 19. Chloroquine, a widely-used anti-malarial and autoimmune disease drug, has recently been reported as a potential broad-spectrum antiviral drug [9, 10]. Chloroquine is known to block virus infection by

increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV. Chinese scientists demonstrated that chloroquine functioned at both entry, and at post-entry stages of the 2019-nCoV infection in Vero E6 cells. They also suggested that besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*. Chloroquine is widely distributed in the whole body, including lung, after oral administration. Chloroquine is a cheap and a safe drug that has been used for more than 70 years and, therefore, it is potentially clinically applicable against the 2019-nCoV [7].

2. **Antibodies:** Antibodies are the critical way to treat the COVID 19. In March the US Food and Drug Administration (FDA) promptly fast-tracked clinical trial approvals, and allowed compassionate use provisions, for a COVID-19 treatment known as **convalescent plasma therapy (CP)**. The treatment involves taking blood from patients, a couple of weeks after they have recovered from a viral infection, and separating out blood cells, leaving just plasma or serum containing immune antibodies. CP therapy was successfully used in the treatment of SARS, MERS, and 2009 H1N1 pandemic with satisfactory efficacy and safety [11]. However, the CP therapy was unable to significantly improve the survival in the Ebola virus disease, probably due to the absence of data of neutralizing antibody titration for stratified analysis [9]. Since the virological and clinical characteristics share similarity among SARS, Middle East Respiratory Syndrome (MERS), and COVID-19, CP therapy might be a promising treatment option for COVID-19 rescue [12].

3. **Vaccines:** After entering to the human body corona virus has only target to enter to the cell by binding with ACE2, through spike proteins and the only way to stop this process is to avoid this binding with the help of antibodies, to this coronavirus is unable to make its copy and we protect from it.

4. **Other Treatment:** Beside the above discussed approaches of treatment of COVID-19, there are some traditional medicines of some of the countries which found to be effective either in the prevention or in the treatment of this disease.

a) **Traditional Chinese medicines:** Apart from these, some traditional Chinese medicines in combination with antiviral or antibiotics are also being evaluated for their effect on the induced infection in humans and mice [15].

b) **Ayurvedic, Yoga and Naturopathy, Unani, Siddha and Homeopathy (AYUSH)**

Treatment: AYUSH system of medication suggests the precautions better than cure, and giving in prima facies that enhancing the body's natural defence system (immunity) plays an important role in maintaining optimum health. Following few suggestions are mentioned as per the traditional immune system boosting approach of AYURVEDA [16].

1. **Take Chyavanprash** 10 gm (1tsf) in the morning. Diabetics should take sugar free Chyavanprash.

2. **Drink herbal tea / decoction (Kadha)** made from Tulsi (Basil), Dalchini (Cinnamon), Kalimirch (Black pepper), Shunthi (Dry Ginger) and Munakka (Raisin) - once or twice a day. Add jaggery (natural sugar) and / or fresh lemon juice to your taste, if needed.

3. **Golden Milk-** Half tea spoon Haldi (turmeric) powder in 150 ml hot milk - once or twice a day.

4. **Nasal application**

(i) Apply sesame oil / coconut oil or Ghee in both the nostrils (Pratimarsh Nasya) in morning and evening

(ii) Oil pulling therapy- Take 1 table spoon sesame or coconut oil in mouth. Do not drink, Swish in the mouth for 2 to 3 minutes and spit it off followed by warm water rinse. This can be done once or twice a day.

Preventive and prophylactic Measures suggested by AYUSH system of Medications:

a) Ayurveda:

Samshamani Vati 500 mg. twice a day with warm water for 15 days The medicine contains aqueous extract of *Tinospora cordifolia*.

b) Siddha:

Nilavembu Kudineer decoction 60 ml. twice a day for 14 days. The medicine contains aqueous extract of *Androgra his paniculata* & others.

c) Unani:

Preparation of decoction by boiling Behidana (*Cydonia oblonga*) 3 gm, Unnab (*Zizyphus jujube*) 5 in number. Sapistan (*Cordia myxa*) 9 in number in water. (Boil these in 250 ml water- boil it till it remains half- filter it — keep in a glass bottle and use it lukewarm). The drugs used in the preparation of this decoction have been reported to have Antioxidant activity, Immuno-modulatory, antiallergic, smooth muscle relaxant activity and Anti-influenza activity. This decoction may be taken twice a day for 14 days. [17]

d) Homoeopathy:

Arsenicum album 30, daily once in empty stomach for three days. The dose should be repeated after one month by following the same schedule till Corona virus infections prevalent in the community.

Current Clinical Trials:

Generally, Regulatory Authority & Ethics Committee Approval: 30-180 days (depending on product type and country). Site Clinical Trials Agreements (CTA): 7 days to 12 months (depending on countries as some countries need Ethics Committee approval date to be included into CTA). Site Activations soon after all everything in place (varies but once all

essential approvals and documents are in place, generally it is done within few days based on hospital team availability) [18].

However, due to Covid-19 circumstances all the regulatory agencies across the globe have changed the policy and expatiated the process of approving the conduct of the clinical trials in following manner:

- Regulatory Authority & Ethics Committee Approval: These are generally coming within 24-48 hours (in some cases within 3 hours or on same days by USFDA).
- Site Clinical Trials Agreements: As soon as approvals are in place, CTAs are being signed on same days (of sending) or within few days by both parties (i.e. sponsor and hospitals).
- Site Activations soon after all everything in place (most activities are being done remotely).

USFDA has created a special emergency program for possible therapies, the Coronavirus Treatment Acceleration Program (CTAP). It uses every available method to move new treatments to patients as quickly as possible, while at the same time finding out whether they are helpful or harmful. They continue to support clinical trials that are testing new treatments for COVID so that to gain valuable knowledge about their safety and effectiveness [19].

Solidarity Trial by WHO:

“Solidarity” is an international clinical trial to help find an effective treatment for COVID-19, launched by the World Health Organization and partners.

The Solidarity Trial will compare four treatment options against standard of care, to assess their relative effectiveness against COVID-19. By enrolling patients in multiple countries, the Solidarity Trial aims to rapidly discover whether any of the drugs slow disease progression or improve survival. Other drugs can be added based on emerging evidence [20].

Conclusion

In the midst of 1960's, first Coronavirus was identified that caused infection in humans, birds and mammals, Severe Acute Respiratory Syndrome (SARS)-CoV and Middle East Respiratory Syndrome (MERS-CoV) wherein former being reported from southern China in 2003 while latter in Saudi Arabia in 2012 respectively leading to a combined death toll of more than 1500 people worldwide. Comparatively, the new pandemic condition caused due to novel coronavirus has led to 27.5 Cr cases and 53.5Cr deaths worldwide till date with the number of cases increasing day by day. However, currently vaccination limits the spreading of infection and deaths but due to the mutation in the virus again raise the alarming condition globally and researchers try to find the solution of new variant named Omicron. However, currently we are still fighting against COVID-19 due to which our conclusions are limited with the only hope that very soon we'll recover from ongoing global public health emergency.

NOTE:

The study highlights the efficacy of "ayurveda" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly used products in our area of research and country. There is

absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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