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CORONAVIRUS TO COVID-19 PANDEMIC: AN OVERVIEW

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ABSTRACT: Coronaviruses wrapped with the layers of positive-sense RNA viruses specified by the club-like projections from their surface responsible for a variety of diseases in the animal kingdom. After the two historical episodes of coronaviruses *i.e.*, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, this time world strike with its highly pathogenic form which is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus disease (COVID-19) is a viral cascade event that starts from Wuhan in December 2019 and becomes a public health emergency of global interest as declared by the World Health Organization. Primarily, bats became an identifiable source of SARS-CoV-2 and their transmission to humans has occurred through an unknown intermediate source. Present situation depicts that more than 200⁺ countries are suffering from the deadly attack of SARS-CoV-2. This virus is dangerous for every age group because of its asymptomatic carrier state that results in acute respiratory diseases. Escalation of this virus occurs very easily through human-to-human transmission *via* droplets or direct contact, with an estimated incubation period of 7-14 days. Fever is the ubiquitous symptom of SARS-CoV-2 followed by a dry cough. After completing more than a 1-year journey with SARS-CoV-2, now the countries are able to fight pharmacologically with this virus. Prevention strategies recommended by WHO and AYUSH include isolation of suspected and confirmed cases with personal hygiene and immunity enhancing measures. This review enlightened on the epidemiology, history of coronavirus, pathogenesis, comparative analysis, clinical features, recent possible pharmacological and non-pharmacological approaches for COVID-19.

INTRODUCTION: Coronavirus (CoVs) comes under the category of zoonotic disease associated with the family coronavirinae and characterized by the jacketed positive-sense RNA viruses with club-like spikes or thorny projection from its surface resulted in numerous pathological conditions in the human and animal world ^{1, 2}.

On the basis of serological studies ^{3, 4} CoVs are segregated into three genera such as Genera I CoVs (animal pathogens) like feline infectious peritonitis virus (FIPV), porcine epidemic diarrhea virus (PEDV), human CoVs HCoV-229E, Transmissible gastroenteritis virus (TGEV) of the pig leads to respiratory infections.

Genera II (veterinary pathogens) such as porcine hemagglutinating encephalomyelitis virus, BCoV, human CoVs, OC43 equine coronavirus and NL63, also developed respiratory infections just like HCoV-229E ^{5, 6}. A genus III (avian CoVs) covers Infectious bronchitis virus (IBV), turkey CoVs, and pheasant CoVs ⁷ **Fig. 1.** On the basis of historical

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expertise, CoVs tragedies were very fateful such as in South China in November 2002, the first outbreak of Severe Acute Respiratory Syndrome (SARS-CoV) collectively touched 8096 people with 774 deaths (mortality rate, 9.6%)^{8, 9}. After that, in September 2012, Saudi Arabia becomes the centralized point for the second outbreak of CoVs, *i.e.*, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), with 2494 confirmed cases and 858 deaths (mortality rate, 34.4%)^{10, 11}. Once again, in December 2019, the world strikes with the third outbreak of CoVs entitled Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) emerged from the Wuhan City of China and rapidly spread across the world^{12, 13, 14}. Novel coronavirus with the asymptomatic features induces pneumonia and designated as coronavirus disease 2019 (COVID-19) as per WHO on 11th February 2020¹⁵. This COVID outbreak is subdivided into four platforms, namely, Platform 1 without the local spread of infection. The cases of infection are limited to those people only who have a travel history from a COVID-19 affected country.

Platform 2: deals with the stage of local transmission from any contact with the infected peoples. Finally, platform 3 is the last stage of community spread¹⁶. It is observed that CoVs attack the human body cells by membrane angiotensin-converting enzyme-2 exopeptidase receptor¹⁷ and associated with symptomatic and asymptomatic states which require immediate hospitalization in the intensive care unit (ICU) due to the virulent and fatal health conditions. Non-Pharmacological approaches such as social distancing, personal hygiene, quarantine, and immunity-boosting measures recommended by WHO and AYUSH become the backbone of this pandemic to fight against this deadly virus.

However, few broad-spectrum antiviral drugs and vaccines have been evaluated against COVID-19 and are under clinical trial^{18, 19}. This overview showed the connectivity between the SARS-CoV, MERS-CoV, and SARS-CoV-2, which may become a milestone creature about the progression history of COVID-19 globally.

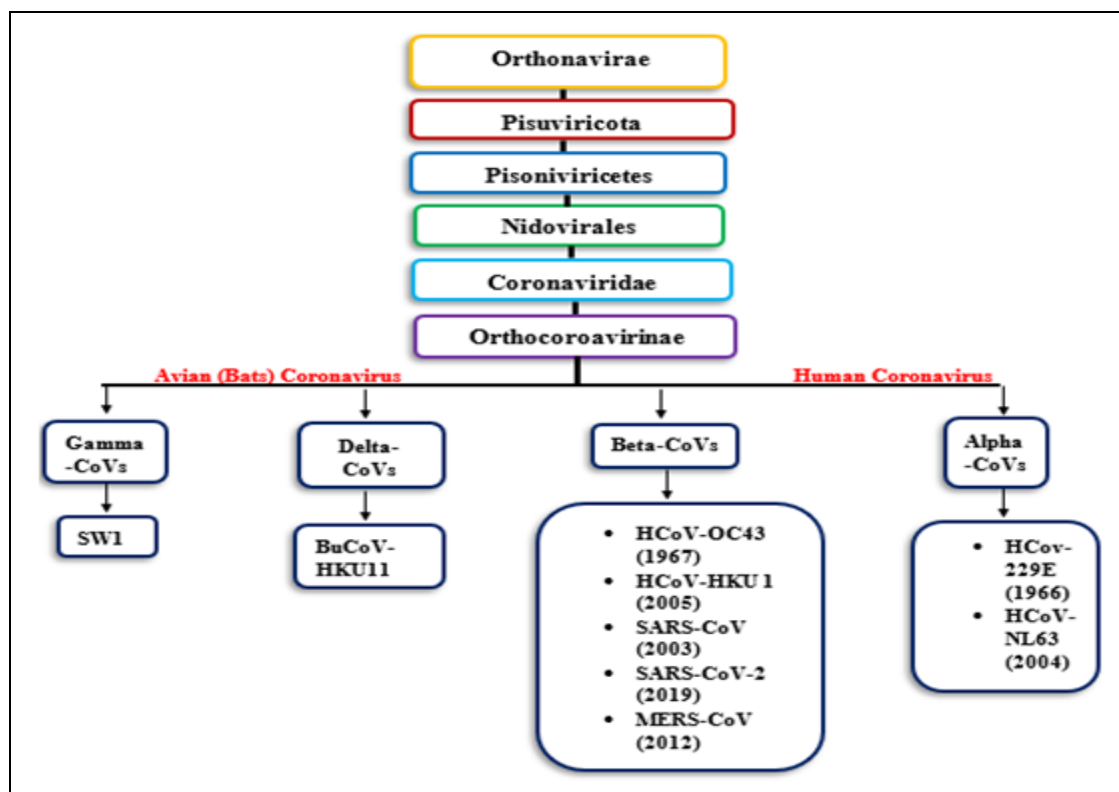


FIG. 1: TAXONOMICAL CLASSIFICATION OF CORONA VIRUSES

2. Epidemiology: COVID-19 pandemic has shown devastating results, and it has affected 107,184,736 million people around the globe, with 2,341,576 reported deaths. On the same side, India has

10,847,790 positive cases followed by 155,195 deaths as cited by WHO as of 10/02/2021²⁰. It has not spared anyone, neither the immunosuppressed nor the healthy ones of the population^{21, 22}. As per

the data of Chinese Health Authorities, COVID-19 has an incubation period of 7 days that ranges from 2-14 days^{23, 24}. Similarly, SARS and MERS CoV incubation period remains commensurate to SARS-CoV-2 *i.e.*, 2-7 days and 2-14 days, respectively. However, the incubation period is smaller in the case of Swine flu and seasonal influenza (1-4 days)^{25, 26, 27}. WHO states that COVID-19 reproductive number (R_0) estimates to be between 1.4-3.5 that makes it highly infectious, and it was observed that lower effective reproductive number (R_0) of SARS (1.77) has led to less spreading and lower pandemic risk^{28, 29}. Moreover, various environmental and physical factors like the type of surface, temperature, and humidity affect its persistence on a variety of surfaces³⁰.

3. Life Cycle of SARS-CoV-2 Virus inside Human Body: Majorly, the constituents for virus structure is proteins especially known as S (spike), E (envelope), M (membrane), and N (nucleocapsid), out of which N protein is involved in the holding of RNA genome while the rest of proteins in combination form the viral envelope^{31, 32}. The S protein namely spike glycoprotein found its role in attaching the virus to the ACE2 enzyme receptor, and ultimately it fuses with the host cell membrane³³. The TMPRSS2 (transmembrane protease serine 2) is used by SARS CoV-2 to

promote priming of S protein and infecting the target cells. Further, the S cleavage site in S protein divides into two subunits *i.e.*, S1 (receptor binding subunit) and S2 (fusion subunit), which facilitates virion attachment and fusion with the cell membrane³¹. However, this cleaving property of S protein is not observed in other species of coronavirus during the molecular analysis, and it is hypothesized that this can be a reason behind more infection power and efficient spreading of the SARS CoV-2 than SARS-CoV^{34, 35}.

Afterward, post membrane fusion, the genetic material of virus (RNA) enters the alveolar epithelial cells and takes over the control of host cell machinery in order to promote viral genome replication and synthesis of polypeptide chains³⁶ which leads to the formation of RCT (Replication-Transcription Complex) which proves to be crucial during the formation of subgenomic RNA as well as structural proteins^{37, 38}. A very important role has been played by the viral envelope in the viral release, its assembly and promotion of viral pathogenesis³⁹. All this has given a brief introduction, but more research is required to understand the role of various smaller viral peptides and subunits which are yet to be described and may prove crucial in better understanding of pathogenic mechanism **Fig. 2**.

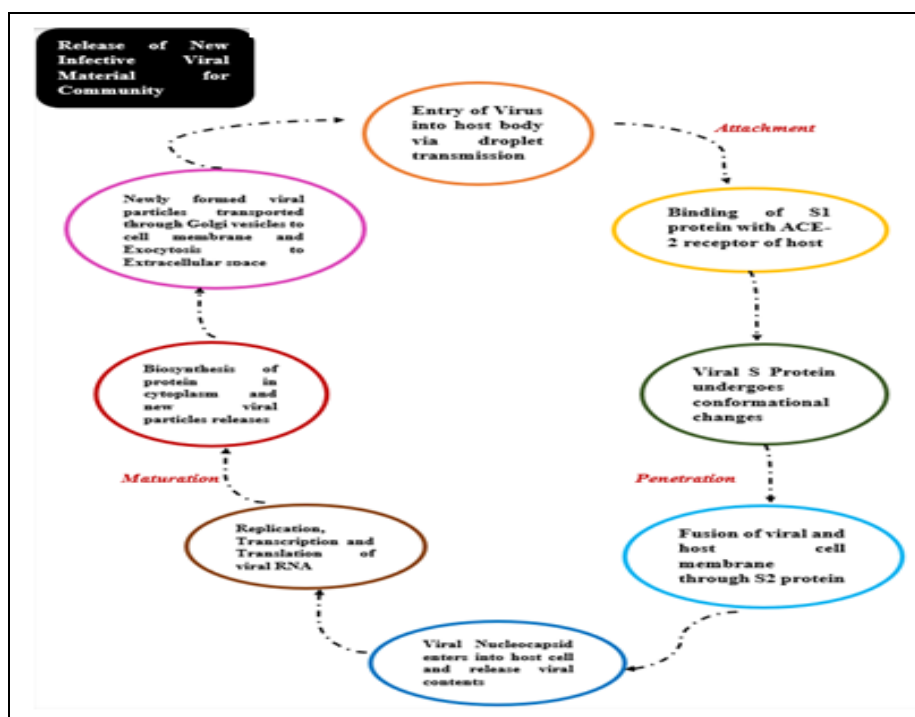


FIG. 2: LIFE CYCLE OF SARS-CoVs-2 VIRUS

4. Disease Pathophysiology: The disease progression can be classified into three phases such as: Phase I (Asymptomatic phase) is the primary stage of infection where virus just enters the human body through a suitable route of transmission but majorly it is through infected aerosols⁴⁰. Virus enters through the nose and infects the nasal epithelial cells where it undergoes replication and propagation followed by infecting ciliated cells in the airways⁴¹. This stage is highly infectious although viral load is less but it can be detected through nasal swabs. The early symptoms are rarely found in this stage and may prove as silent killers⁴². Phase II (Infection of the upper respiratory tract) is the symptomatic stage where symptoms like dry cough, high fever, malaise *etc.* starts appearing. In this stage, virus has reached the upper respiratory tract owing to which immune response has been generated by the body against the virus particles⁴³. The virus infected cells start releasing C-X-C motif chemokine ligand 10 and interferon mainly IFN-beta and IFN-alpha. This immune response is capable of preventing further replication of virus in four-fifth of the population⁴⁴. Phase III (Infection in lower respiratory tract) is the critical stage and progression is seen in only one-fifth of the patients and patients start developing severe symptoms. This is recognized by the invasion of viral particles into the type 2 alveolar epithelial cells and undergoes replication over there so as to produce the large amount of viral nucleocapsids⁴⁵. Pneumocytes got fully filled with virus copies and starts releasing a good amount of pro-inflammatory cytokines like IFN- α , IFN- γ , IL-1 β , IL-6, IL-12, IL-18, IL-33, TNF- α , TGF- β , *etc.* and chemokines CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, *etc.* which looks like a storm of cytokines. Further, these attract some neutrophils mainly CD4 and CD8 T cells which starts sequestering in the tissues of lungs⁴⁶. They try to fight with the virus but in that action, they harm lung tissues that further results in apoptosis of the cells and release of new viral cells, which further starts infecting surrounding epithelial cells⁴⁷. Due to the autoimmune action of sequestered inflammatory cells, there is an injury at the gas exchange surfaces of the alveoli that leads to ARDS (Acute Respiratory Distress Syndrome)⁴⁸.

5. Transmission and Clinical Features: The transmission for COVID19 can be categorized into

three general routes: Droplet transmission which is P2P (person to person) transmission in which infected person who is constantly coughing and sneezing produces droplets full of viral load and which came in close proximity of the mucosal surface (eyes, nose, mouth) of the healthy person⁴⁹. Contact transmission occurs by sharing of fomites like clothes, utensils, furniture, medical equipment like thermometer with the infected person⁵⁰. Lastly, Air borne transmission or aerosol transmission is the one in which various aerosol generating operations like bronchoscopy, nebulization with oxygen, endotracheal incubations, CPR *etc.*, are performed for or by an infected person without taking preventive measures⁵¹. COVID-19 generally infects people of all age groups but people of age 40-70 years are more prone to it^{11,26}. The early and common symptoms are high fever, dry cough, severe body ache, difficulty in breathing, malaise, vomiting, disturbed abdomen⁵². In the mild condition, pneumonia starts developing with excessive coughing and breathlessness. However, in severe cases symptoms are severe pneumonia followed by hypoxia, acute kidney injuries, ARDS along with shock, encephalopathy, cardiac failure *etc.* can be noted down⁵³. Rhabdomyolysis, aspergillosis, pancreatitis, neurological complications are some of the rare complications involved in COVID-19⁵⁴. Various diagnostic tests based upon epidemiological history, auxiliary examination and clinical manifestation are designed in order to have the early detection and further spreading can be prevented. RT-PCR (rapid test polymerase chain reaction) testing detects the nucleic acid of the viruses⁵⁵, ELISA test is based upon antigen antibody reaction which is used for confirmatory purposes, Point-of-care testing (POCT) is done for identification of IgG/IgM⁵⁶, CT scan and X Rays are to detect the presence of glass opacities and bilateral patches of cough and blood test can also be performed which shows lower white blood cell count and increased level of creatine protein, aspartate, aminotransferase, creatine kinase *etc.*⁵⁷

6. Corona Virology from Sars to Mers: The CoVs comes in limelight in 1968, fabricated from the crown like morphology⁵⁸. They are sorted into four sister branches: α -coronavirus (α -CoV), β -coronavirus (β -CoV), δ -coronavirus (δ -CoV) and γ -coronavirus (γ -CoV)^{59,60}. Targeting towards its

pathogenicity, CoVs are of two types ⁶¹ *i.e.* Low pathogenic (229E, HKU1, OC43, NL63) and high pathogenic (SARS and MERS) that cause multiple human diseases in the upper and lower respiratory tract respectively ^{62, 63}. Basically, the SARS-CoV-2 is layered with single positive-stranded RNA with its genomic range from 26 to 32 kilobase pair in length ^{58, 64}. As per genetic screening, SARS-CoV-2 is closely related with (88–89% similarity) two bat-derived SARS-like CoVs species, namely bat-SL-CoVZC45 (Gen Bank accession no. MG772933.1) and bat-SL-CoVZXC21 (Gen Ban accession no. MG772934.1), and it is clearly segregated from SARS-CoV (~79% similarity) and middle east respiratory syndrome coronavirus (MERS-CoV) (~50% similarity) ^{65, 66}. From asymptomatic to symptomatic state, the SARS-CoVs is a life-threatening condition that resulted in acute respiratory distress syndrome, multisystem organ failure and finally death ⁶⁷. The severity outcomes of SARS-CoV-2 are much more than SARS-CoVs ⁶⁸ because of the length of (S) proteins, therefore its receptor-binding compatibility is totally different and modified from SARS-CoV ⁶⁹. Moreover, the nucleocapsid (N) protein in SARS-CoV helps to neutralize the immunological responses of the host and showed the antagonistic activity against interferon-gamma (IFN- γ), basically a cytokine that triggers macrophages but still suspense should be there in the case of SARS-CoV-2 *i.e.*, its N proteins shows this ability or not ⁷⁰. Meanwhile, SARS-CoV-2 stands with 2 to 3-time higher R trough value (R_0) in comparison with SARS-CoV (<1). So, it become highly diffusible form of infection with a long incubation period associated with mild-to-moderate symptoms of infection with low mortality rate ⁷¹. SARS-CoV and MERS-CoV both belongs from the zoonotic class of virus with their possible roots of origination in bats and camels ^{72, 73}. The intensity of spreadability of CoVs differs in every age group like SARS-CoV affects the young population whereas MERS-CoV affects the people above 50 years of age, however, SARS-CoV-2 touched with their harmful effects to people of every ages ^{74, 75}.

7. Preventive Approaches:

Pharmacological Approaches: Drugs, Vaccines.

Non-Pharmacological Approaches: Quarantine and Social Distancing, WHO preventive guidelines,

Ayurvedic, Yoga and Naturopathy, Unani, Siddha and Homeopathy (AYUSH) guidelines.

7.1. Pharmacological Approaches:

7.1.1. Drugs: Yet now, there is no approved treatment for COVID-19 so based upon the previous experience with SARS-CoV and MERS-CoV, it gives us direction towards antiviral drugs such as Ribavirin, Lopinavir, and Ritonavir ⁷⁶. In recent times Chloroquine has been found to have *in-vitro* anti-COVID-19 activity by showing its action at both entry and post-entry stages of virus ⁷⁷.

Chloroquine has been well illustrated with *in-vitro* effects on inhibition of uncoating or alteration of post-translational modifications of newly synthesized proteins, especially inhibition of glycosylation in numerous viruses ⁷⁸. Therefore, Chloroquine and Hydroxychloroquine may be the future drug for treating COVID-19 infection, although many clinical trials with these drugs are already underway ⁷⁹. However, Remdesivir only and along with Chloroquine or interferon beta, significantly blocked the SARS-CoV-2 replication, and patients were declared as clinically recovered ^{80, 81}.

A short while ago, Physicians isolated the blood plasma from clinically recovered patients of COVID-19 and injected it in the infected patients who showed positive results with rapid recovery ⁸². Plasma therapy may be good futuristic potential candidates for COVID 19 patients after repeatedly clinical successful outcomes.

7.1.2. Vaccine: After the advent of coronavirus, a huge competition was noticed among various institutes in the search of suitable vaccine candidate for this deadly virus. Maximum of them targets the S glycoprotein of SARS-CoV-2 ^{78, 80}. During December 2020 and January of 2021, various nations started the vaccination drive at a large scale after the successful testing of vaccines and taking approval from the drug regulatory authorities.

Out of hundreds of candidates, some of them, like Comirnaty, Moderna COVID19 vaccine, Coronavac, Astra Zeneca, SputnikV, Covaxin, EpiVac Corona have shown excellent results during preclinical as well as clinical trials and are now used by various nations **Table 1** ⁵⁸.

TABLE 1: VARIOUS POTENTIAL CANDIDATES OF COVID-19 VACCINE

S. no.	Category	Name of Vaccine	Manufactured by	Chief point
1	Protein sub unit vaccine	NVX-CoV2973	Emergent BioSolutions, Novax, Inc	Based upon the recombinant expressions of the stable pre-fusion, coronavirus S. Protein
		Molecular Clamp Stabilised spike protein vaccine	University of Queensland in collaboration with GSK and Dynavax	Based upon the Molecular Clamp technology
		PittCovace	University of Pittsburgh	Micro-Needle Array (MNA) based recombinant SAR-CoV-2 vaccine
2	Viral Vected vaccines	Triple Antigen Vaccine AdS-nCoV	Premas Biotech, India	Multi-antigenic VLP vaccine prototype
		Coroflu	CanSino Biologic Inc, Beijing Institute of Biotechnology	Constructed using the Admax system from the Microbix Biosystem
			University of Wisconsin Madison, FluGen, Bharat Biotech	The vaccine express the hemagglutinin protein of the influenza virus
3	mRNA Vaccine	ChAdOx1 mRNA-1273	University of Oxford	Recombinant adenovirus vaccine
		BNT162b1	Moderna TX, Inc	mRNA encapsulated in Lip[id nanoparticle
			Biotech FosunPharma Pfizer	mRNA encapsulated in 80nm ionizable cationic lipid nanoparticles
4	DNA Vaccine	INO-4800	Inovia Pharmaceuticals	Use codon optimized S protein sequence of SARA-CoV-2
		ZyCoV-D	Zyodus Cadila	Genetically engineered DNA plasmid-based vaccine encoding for the membrane proteins of the virus
5	Live Attenuated Vaccine	DeINSI-SARA-CoV-2-RBD	University of Hong Kong	Re-organized to express the RBD domain of SARA-CoV-2
6	Others	BBV152 (A-C)	Bharat Biotech, ICMR, NIV	Inactivated whole virion vaccine

7.2. Non-Pharmacological Approaches:

7.2.1. WHO Quarantine Guidelines and Social Distancing:

The ultimate goal of quarantine is to restrict the movement or separate the rest of the population from the healthy persons who may have been exposed to the virus and to monitoring their symptoms and ensure early detection of cases⁸³. Quarantine differs from isolation as it separates ill or infected persons from others to prevent the spread of infection or contamination. Persons who are in quarantine must be placed inappropriately ventilated, the spacious room having the provision of adequate food, water, and hygiene facilities⁸⁴. Social distancing (at least a distance of 1 meter) must be followed; along with this, medical assistance and psychosocial support must be there. According to WHO, the quarantine period for COVID-19 cases should be 14 days⁸⁵. Ministry of Health and Family Welfare, Government of India and other countries have published travel advisories from time to time respectively which focus on the people with travel history from China, and other affected countries will be quarantined on arrival⁸⁶. Diamond Princess, a cruise ship docked off Yokohama in Japan was quarantined for two weeks after a tourist who stepped out at Hong Kong tested positive for SARS-CoV-2^{87,88}. The cruise ship had over 3,700 passengers and crew, of whom 705 were tested positive for SARS-CoV-2⁸⁹.

7.2.2. WHO Guidelines for Prevention of Covid-19:

A string of measures has been suggested to diminish nosocomial infection, including training for prevention and control, isolation, disinfection, classified protections at different degrees in infected areas and protection of confirmed cases^{90,91}. Personal hygiene, a healthy lifestyle, and adequate nutritional intake are the main ways to boost up immunity^{92,93}. According to studies, vitamin C may hinder the susceptibility of lower respiratory tract infection under certain conditions in COVID-19⁹⁴. For SARS-CoV-2 infection protective measures include improving personal hygiene, wearing medical masks, proper rest, and good ventilation^{95,96}. Health care workers are endorsing to use of particulate respirators such as those certified N95 or FFP2 while performing aerosol-generating procedures as per WHO guidelines⁹⁷. From the experience of management of MERS-CoV and SARS-CoV infections, the WHO recommended infection control interventions to reduce the general risk of transmission of acute respiratory infections by avoiding close contact with infected people, practicing cough etiquette and frequent hand washing along with sanitization^{98,99}.

7.2.3. Ayush Guidelines: Ministry of AYUSH guidelines gives the green light to the following self-care guidelines for preventive health measures

and boosting immunity with special reference to respiratory health¹⁹. As there is no medicine for COVID-19, so it will be advisable to take preventive measures because prevention is better than cure.

7.2.3.1. General Measures: Drink warm water throughout the day. Daily practice of Yogasana, Pranayama and meditation required for at least 30 minutes. Spices like Turmeric (*Curcuma longa*, Family *Zingiberaceae*), Cumin (*Cuminum cyminum*, Family *Apiaceae*), Coriander (*Coriandrum sativum*, Family *Apiaceae*), and Garlic (*Allium sativum*, Family *Amaryllidaceae*) are recommended in cooking¹⁹.

7.2.3.2. Ayurvedic Immunity Promoting Measures: Take Chyavanprash 10gm in the morning. Diabetics should take sugar-free Chyavanprash. Following are the major ingredients of Chyavanprash: Amla (*Phyllanthus emblica*, Family *Phyllanthaceae*), Sesame oil (*Sesamum indicum*, Family *Pedaliaceae*), Cow's ghee (Clarified butter), Sugar, Honey, Agarwood (*Aquilaria malaccensis*, Family *Thymelaeaceae*), Bael (*Aegle marmelos*, Family *Rutaceae*), Dry grapes (Vitaceae), Long pepper (*Piper longum*, Family *Piperaceae*), Red sandalwood (*Pterocarpus santalinus*, Family *Fabaceae*), White sandalwood (*Santalum album*, Family *Fabaceae*), Cardamom (*Elettaria cardamomum*, Family *Zingiberaceae*), Tejapata (*Cinnamomum tamala*, Family *Lauraceae*), Guduchi (*Tinospora cardifolia*, Family *Menispermaceae*), etc. Drink herbal tea/decoction (Kadha) made from Basil (*Ocimum sanctum*, Family *Lamiaceae*), Cinnamon (*Cinnamomum verum*, Family *Lauraceae*), Black pepper (*Piper nigrum*, Family *Piperaceae*), Dry Ginger (*Zingiber officinale*, Family *Zingiberaceae*) and Munakka (Raisin) - once or twice a day. Add jaggery (natural sugar) or fresh lemon juice to your taste, if needed. The Golden Milk- Half teaspoon turmeric (*Curcuma longa*, Family *Zingiberaceae*) powder in 150 ml hot milk may be taken once or twice a day¹⁹.

CONCLUSION: Worldwide, this pandemic year 2020 becomes familiar to everyone as a year of COVID-19 or coronavirus. Every day of this year starts with the new outcomes of this deadly virus on human health and becomes an invisible health blackmailer to all ages in the existing universal

population. Although, the countries with outstanding health care facilities and infrastructures are break down with the footprints of COVID-19. So, our first priority is to stop the progression or transmission of this deadly virus with the use of very familiar coronavirus terminologies such as isolation, quarantine, immunity, and personal hygiene maintains. This review enlightens coronavirus's life story, including its complicated pathogenicity to genomic similarities with other forms of CoVs and the newly discovered vaccines. Therefore, it's fascinating to gather knowledge about the linkage of these trios of CoVs, i.e., SARS-CoV, MERS CoV, and SARS-CoV-2, and that may also become the ray of hope for designing new antiviral therapies. This present overview also focused on the currently used pharmacological and non-pharmacological criteria's in India or worldwide as well as on the active, recovered, or death cases of coronavirus. On behalf of gathered information, it's clear that for eradicating this corona term, we should work on a ground level, develop an advance or scheduled framework in our health care system to stop the progression or control of this virus. This present eugenically framed molecular level study of CoV to COVID -19 may act as good potential candidates for futuristic researchers in the field of corona virology worldwide.

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