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REVIEW PAPER

Multidisciplinary therapeutic potentials of dietary nutrients in combating COVID-19 pandemic

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ABSTRACT

A novel coronavirus (SARS-CoV-2) has rapidly spread from a regular seafood market in Wuhan, China to more than 200 countries, globally infecting millions of people with a dangerous pneumonia like fatal conditions. Depending upon the immunity of individual, the severity of infection and its viral load, symptoms varied from mild to severe leading to Acute Respiratory Distress Syndrome (ARDS) and sepsis. Thus, in order to combat the symptoms and reduce the death rate it was accepted globally to use pre-used anti-viral, anti-malaria, anti-inflammatory and various immune-boosters drugs. The drugs are undergoing clinical trials to increase its safety efficiency simultaneously suppressing viral infection. Along with drugs, the micronutrients like vitamin C, vitamin D and Zinc are also used as immune-boosters in combination with drugs to increase the efficiency rate and reduce the side effects. Following review, describes the clinical trials currently undergoing and importance of micro-and macro nutrients to overcome hyper-inflammation and cytokine storm generated by SARS-CoV-2.

Keywords: SARS-CoV-2, vitamin C, vitamin D, zinc

1. INTRODUCTION

At the ending of the second decade of 21st century, a global pandemic spread across the world. Terrifying as it may appear, it has engulfed 14.6 million confirmed populations as of now and it continues to grow exponentially with 3.09million deaths as recorded, till date. The World Health Organization (WHO) named the pandemic virus as COVID-19 which as reported, was thought to spread from a sea-food market, Wuhan, China via bats [1], snakes [2] and pangolins to humans [3-4]. On 11 March 2020, WHO observed a notable 13-fold increase in the number of cases outside China along with threefold increase in the number of countries with cases, declared COVID-19 as pandemic situation [5]. Later it was found that COVID-19 has 75% similar homology with severe acute respiratory syndrome- corona virus (SARS-CoV), an epidemic that occurred in 2002-2003. Thus the International Committee on Taxonomy of

Viruses (ICTV) and other virologists renamed it SARS-CoV-2 [6-7].

Although SARS-CoV shares genetic similarity with SARS-CoV-2 but the mortality rate of SARS-CoV is much higher compared to SARS-CoV-2. Therefore, SARS-CoV-2 is only lethal due to its infectious nature and quick replication. It has spread from China to further 180 countries via transport and other trading ways causing chaotic imbalance among economic and health facilities globally. With fast the spread of disease, the major focus lies on treating affected population to cease the fatality rate to minimum and controlling its preventing it to affect the remaining population.

In such desperate times, the doctors and researchers globally decided to use pre-used clinically tested and safe anti-viral drugs, anti-malarial drugs, anti-inflammatory drugs and immune-modulators to boost the immune system against SARS-CoV-2 hyper inflammation and cytokine storm. Along with the drugs, it was found the crucial role of micronutrients like vitamins and minerals, which although are needed in least amount but they play major roles in boosting and supplementing immune system. The various micro-nutrients undergoing clinical tested are vitamin D, Vitamin C, Zinc, Selenium, Copper, and Iron. Therefore, let us further discover more on how drugs and micro-nutrients are can be potential candidates for therapeutics against SARS-CoV-2.

2. CORONA VIRUS- STRUCTURE, REPLICATION

For better understanding of the action by various drugs available for treatment, one must get thorough the knowledge of COVID-19 structure, replication and its related function. Corona virus, like other viruses have an amazing architectural build-up of proteins protecting the nucleic acid inside the capsid and other proteins for its dwelling on host and completing its replication cycle. Their name was coined by June Almeida and David Tyrrell in 2002, while studying human corona viruses when they encountered that these new viruses have a kind of halo structure surrounding them like “crown” in Latin or “garland” in Greek language [8-10]. These are large about 125 nm in diameter with envelope diameter of about 85 nm, spherical (not exactly) in shape covered with surface viral spike (20 nm long) with pelpomers protein all over it to give it a crown like appearance [11-12]. Coronaviruses come under the Coronaviridae in the order Nidovirales and are classified into four genera (figure 1) [13-14].

Corona viruses are positive, single strand RNA with one of the largest genome size varying from 26 to 31 kbp [15]. Their genomic organization is 5′-leader-UTR-replicase (ORF1ab)-spike (S)-envelope (E)-membrane (M)-nucleocapsid (N)-3′UTR-poly (A) tail, [12] (figure 2). Among 8-10 open reading frames (ORFs), ORF1a and ORF1b undergo translation to produce replicase-transcriptase protein, RNA-dependent RNA polymerase (RdRp), contained in 16 non-structural protein which functions for both transcription and replication of RNA from RNA strand. And while during replication, the other accessory and structural

proteins essential for its survival are released to complete its viral replication cycle; Spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins [16-17]

For Coronavirus, the ratio of E:S:M is approximately found to be 1:20:300 [18]. Among the three, M and E are responsible for maintaining structural shape and forming viral envelop, together to form a viral assembly. The N protein forms the capsid around the nucleic acid of the virus, thus it plays a major role in diagnostics. The S proteins are the bulbous projection that impart crown like appearance to virus and these projections are made up of three parts: a large ectodomain, a single-pass transmembrane anchor, and a short intracellular tail. They plays significant role in inducing host immune response by receptor binding and membrane fusion via its homotrimer structure consisting of S1 and S2 subunit.

The S1 forms the head with receptor-binding domain (RBD), the most complex and crucial element of CoV and the S2 forms the stems which anchors the host cell on membrane fusion. The S protein binds host cell membrane with its protein receptor named angiotensin-converting enzyme 2 (ACE2), which is a type I membrane protein that is expressed in nasal mucosa, bronchus, lung, heart, esophagus, kidney, stomach, bladder, ileum and mainly associated with cardiovascular diseases [19-20]. Thus, ACE 2 plays a significant role in human body. It was found that SARS-CoV's RBD is found to be linked with humans, ferrets, cats and other highly-receptor-homologated animals with elevated ACE2 affinity, since RBD contains 6 amino acids important for ACE2 at the various co-ordinates L455, F486, Q493, S494, N501 and Y505, when compared to SARS-CoV [21-22]. The spike protein binds the host cell with the help of TMPRESS2 (transmembrane protease serine type 2), the much lesser focused component which allows virus fusion with the SARS-CoV-2 infected cell and its activation by cleavage of virus protein [23-24].

With this little known information, the researchers were able to decipher how these viruses could have affected human from animal like bat to cause a pandemic. According to one of the theories, the crucial polybasic cleavage location at S1-S2 junction responsible for inducing host immune response contain 12 nucleotides that may have undergone mutations, insertions and removals of nucleotides. Thus, in order to create a pandemic situation, the virus requires animal host in bulk amount and a ACE2 gene closest to human life for the virus to complete its evolutionary cycle with it essential polybasic cleavage site and spike protein binding human ACE2 [24]. And now in present scenario, the virus jumps from one person to another adapting itself to the human body leading to serious illness or death, depending upon the immunity of the individual [25].

2.1. Spread

Although it was earlier believed that bats were the epicenter of spreading SARS-CoV, but later it was found that they cannot directly infect humans unless they undergo mutation or recombination in animal hosts like civets,

pangolins. Thus, to verify this mystery, history of MERS-CoV and SARS-CoV was searched and we found that civets and camels, respectively, were their carrier. Applying the same on SARS-CoV-2, its genome was found to be 99% similar to pangolin origin, thus it was suggested that it may have spread via bats to pangolins to human [26]. This information helps in prevention and control of SARS-CoV-2 in China.

SARS-CoV is spreads via human to human direct contact or cough/sneeze droplets within a space of 6 feet or indirectly via the contaminated surfaces like floors, furniture that rubs against hands to ears, eyes or nose [27]. This was possible only due to its certain physiochemical properties that allowed it to remain alive. They remain unaffected by mild UV radiation, high temperatures up to 56 ◦C for 30 min and are more stable on plastic and stainless steel [28]. But on the bright side, they are sensitive to disinfectants such as diethyl ether, 75% ethanol, chlorine, per acetic acid, and chloroform and they are less stable on copper and cardboard [28-29]. It was found that on cardboard, the half-life of SARS-CoV-2 was longer than that of SARS-CoV and the longest viability of both viruses was on stainless steel and plastic [29]. Thus, the main route of transmission is majorly the respiratory droplets and contact transmission.

2.2. Symptoms

As the human encounters the virus, primary infection occurs in the mucosal epithelium of upper respiratory tract (nasal cavity and pharynx) and it further divides and multiplies itself to lower respiratory tract and gastrointestinal mucosa [30]. Therefore, some studies suggest that SAR-CoV-2 can be detected in urine and stool laboratory samples, indicating fecal-oral transmission [28].

Further, as we also know that the ACE-2 receptor is located on major organs like heart, kidney, and lungs, thus binding of SARS-CoV-2 to these organs generate unwanted signals leading to disastrous conditions like cardiac disorder, abnormal vomiting etc. Due to pathogenic invasion, the immune system gets activated to kill pathogens by producing inflammatory molecules like IL-6, IL-1, TNF-α. Sooner or later, this inflammation becomes aggressive due to rapid viral replication, antibody dependent enhancement (a suggested mechanism for viral infection), ACE-2 down-regulation (causes dysregulation of renin-angiotensin system (RAS) leading to pulmonary damage) and cellular damage, and this condition is termed as cytokine storm [31-32]. It has been reported that severe case of SARS-CoV-2 infections lead to hypoxia, sepsis and Acute Respiratory Distress Syndrome (ARDS). Sepsis is inflammation of the body organs caused due to exotic chemicals secretion in the bloodstream leading to multiple organ failure while ARDS is the hypoxia condition of lungs leading to acute lung injury and other respiratory disorders [33]. These both are potential life threatening events generally seen as clinical indication during severe pneumonia.

Symptoms vary from one person to another due to individual's strong or weak immune system affinity with CoV–S protein. Some people are asymptomatic, i.e, although they are infected but they do not show any symptoms related to

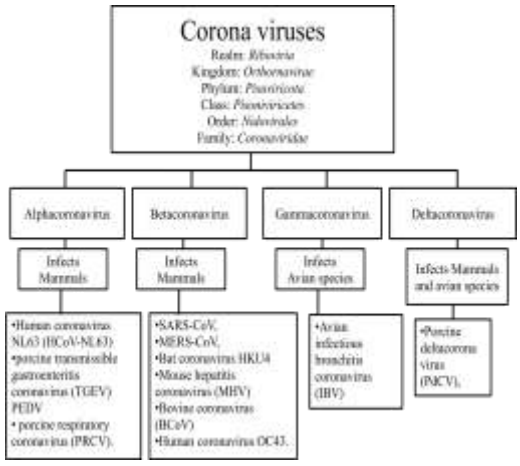

Figure 1. Classification of Corona viruses

the CoV, while some show mild to serious symptoms, as categorized by WHO [34].

It is seen that with careful management of disease, the symptoms may go away in 14 days. But after treatment, it's the major responsibility of the patient to take care of themselves to avoid a second round or jump of the previous infection, since till now the vaccines and drugs to completely treat it are in clinical trials.

3. ROLE OF MICRO-NUTRIENTS IN TREATMENT

Researchers all over the world are equipped with clinical trials on the existing anti-viral, anti-malarial drugs etc., and so on, but the only role that can be played at an individual level to boost immune system and prevent infection is by proper intake of diet supplied with balanced amounts of micro- and macro- nutrients like vitamins, minerals, carbohydrates, proteins and fats. It has been well- established by various studies that micronutrients (Vitamin A, B, C, D, E, Zinc, Copper, iron, magnesium, and selenium) affect every stage of immune system: innate immunity, adaptive immunity, inflammatory response linking innate and adaptive immunity and various other chemical responses. Thus, their deficiencies in anyway either intake or reduced absorption by body itself, may lead to severe weakening of the immune system.

With the SARS-CoV-2 outbreak, it has become an essential requirement of all humans to meet their nutrient uptake threshold to avoid infection, as already discussed lower immunity is one of its risk factors. Among many micro-nutrients it has been found that there are specific micro-nutrients that enrich our immune system along with their anti-viral activity, like Zinc, Vitamin D, Vitamin C, while selenium, iron , copper are still considered as side options. But the earlier three, have already shown their anti-viral activity in past against HIV, influenza and Ebola. Let us further get to know the details of how have they been targeted for COVID-19 treatment.

a. Zinc

This micro-nutrient maybe needed in very less amount for proper functioning of our body as it is involved in the activation and inactivation of various essential enzymes and co-enzymes that are responsible for vital cellular functions, including energy metabolism, DNA synthesis, RNA transcription, anti-oxidant effects against ROS and reactive nitrogen species etc [35-36]. The main sources of food supplemented with good amount of zinc are dark chocolate, meat and seafood (such as lamb, beef, chicken, oyster, and lobster), Black rice, black sesame, soy foods, mushroom, celery, legumes, lentils, nuts, sunflower seeds, and almonds [37].

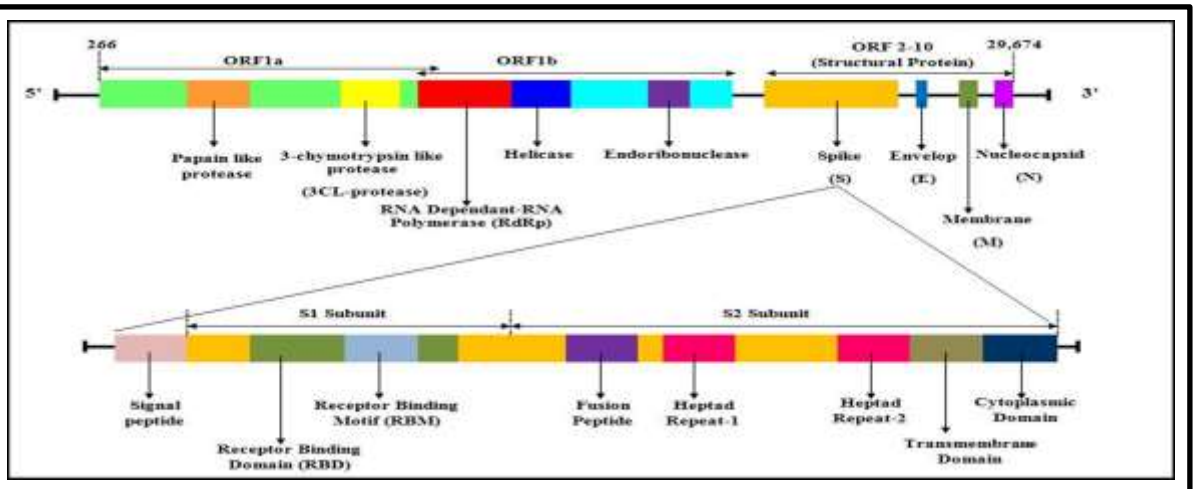

Figure 2. Genomic organization of SARS-CoV-2 with expanded S1/S2 subunits of S protein

Zinc is considered as a gateway for immune system. Beginning with they provide the structural physical barrier by maintaining the integrity of skin and mucosal membrane by acting it like co-factor for metalloenzymes required for cell membrane repair [38]. Further, participate in enhancing and maintaining NK cell cytotoxic activity improves phagocytic capacity of monocytes and involved in complement activity [39-41]. Besides these important roles, in these pandemic SARS-CoV-2 time, zinc functions as Anti-inflammatory agent, which aids in production of IFNγ, modulate the cytokine production by suppressing development pro-inflammatory Th17 and Th9 cells and control the production of such as IL-2, IL-6, and TNF-α, which are majorly responsible for cytokine storm and hyper-inflammation [39, 42-48].

It may not be hard to believe that zinc is undergoing trials for it anti-viral response towards SARS-CoV-2, since it has shown a 42% common cold or rhinovirus infection reduction with higher doses of Zinc, as estimated [49-50] Previously, during the influenza outbreak, zinc and its related forms like salts, ionophores have shown antiviral activities in-vitro by reducing the viral replication potential [51]. Zinc has been known to reduce the hepatitis C virus infection and simultaneously, help the other anti-viral treatments to increase its efficacy in patients [52]. It's known to increment the treatment of human papillomavirus (HPV) generated cutaneous and genital warts [53-54]. Likewise, zinc salts (sulphate and acetate) are known to block the RdRp, viral gene significant for replication in hepatitis E [55]. Finally, various forms of zinc like its ions, ionophore and pyrithione have been investigated to find that they significantly reduce the SARS-CoV infection by inactivating the RdRp, and since it has already been discovered that SARS-CoV-2 shares more than 70% homology, it has been suggested to use zinc as a potential drug [56].

Thus, as per recommendation it is said human body requires 40mg/day as its daily uptake, and doses higher between 200-400mg/day can lead to adverse effects, including nausea, vomiting, epigastric pain, lethargy, and fatigue [57].

b. Vitamin C

Table 1. Summary of Sars-CoV-2 with symptoms

Condition	Symptom	Features	Quick response
Mild	Common	Fever, dry cough, tiredness.	Healthy people may manage themselves at home; otherwise seek a doctor's advice
Moderate	Less common	Aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on skin, or discolouration of fingers or toes.	Go for SARS-CoV diagnostic testing centre to test positive or negative reports relating it.
Severe	Confirmed	Difficulty breathing or shortness of breath, chest pain or pressure, loss of speech or movement. Constant fever.	Immediately Seek medical attention

Vitamin C or ascorbic acid is an essential water soluble vitamin with a daily uptake requirement of 90mg. Since it is not stored in the body, there are various citrus juicy food items like lemons, oranges, Broccoli, Brussels sprouts, and cauliflower, Green and red peppers, Spinach, cabbage, turnip greens, and other leafy greens, Sweet and white potatoes, Tomatoes and tomato juice and Winter squash. Its deficiency lead to bleeding gums, frequent bruising and infections, poor wound healing, anemia and scurvy.

Considering the SARS-CoV-2 outbreak, the immune system has been declared at risk due to increased inflammation and cytokine storm, which bombards immense amount of free radicals in the body causing oxidative damage of brain, heart and lungs. Since these organs are aerobic in nature, their oxidative damage leads to decline in health. Besides being an excellent anti-oxidant and co-factor in significant physiological processes like hormone production, collagen synthesis, connective tissue, bones, teeth, small blood vessels and immune potentiation, it also participates as an anti-viral agent [58-59].

It has been suggested that vitamin C modulates immune system by up-regulating the production of α/β interferons and decreasing the production of pro-inflammatory cytokines [60]. There have been various experiments that explain the significant role of vitamin C against influenza, herpes virus, poliovirus, Venezuelan equine encephalitis, human lymphotropic virus type 1 (HTLV-1), human immunodeficiency virus (HIV), parvovirus and rabies virus. In 2018, a study show that patients suffering from severe pneumonia were supplemented with three things; vitamin C, thiamine and hydrocortisone, indicated better outcome and improved lung scans by vitamin [61]. Another randomized control trial in 2019, indicated that vitamin C has no effect in the treatment of sepsis and severe acute respiratory failure, also some people died in the group receiving treatment [61]. Finally in 2020 a meta-analysis of nine existing clinical trials consisting of two groups; patients receiving vitamin C intraveneous transfusion IV and others not, suggested that mechanical ventilation length decreased by 14%, but results varied among various studies [61]. Therefore, although the properties of vitamin C sound beneficial during this outbreak but evidently, there are no such studies indications their role in treating or curing COVID-19 patients.

c. Vitamin D

Vitamin D is a fat-soluble vitamin stored in adipose tissue where by a process called hydroxylation through liver and kidney it convert itself from ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3) to calciferol. The main source of vitamin D is sun while the foods supplemented with high amount of vitamin D are flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils, while smaller amounts can be found in beef liver, milk, cheese, and egg yolks.

Vitamin D has established significant roles in calcium and bone homeostasis, while other major roles are cell growth, regulating insulin levels and supporting diabetes management, supporting lung function and cardiovascular health, influencing the expression of genes involved in cancer development and regulation of inflammation by enhancing the pathogen fighting effect of monocytes and macrophages (white blood cells) to decrease inflammation. Vitamin D receptors are expressed on B cells, T cells and antigen presenting cells, thus dysregulation or deficiency of vitamin D may lead to many immunological disorders like auto-immune diseases. It regulates both cellular and adaptive immunity by modulating INF- and tumor necrosis factor α and inhibiting T helper cell type 1 responses and stimulating of T cells induction, respectively [62-63].

Vitamin D deficiencies has also been linked to many manifestations of SARS-CoV-2 like ARDS, cardiac arrest and reduced lung functions and are also associated with respiratory diseases, including tuberculosis, influenza, asthma, and chronic obstructive pulmonary disease (COPD), as well as viral and bacterial respiratory infections [62, 64]. Studies conducted suggest that vitamin D in serum were inversely associated with pro-inflammatory cytokines, IL-6, increased CRP, and increased risk of pneumonia, ARDS, diabetes and heart failure [65-71]. Thus there are various clinical trials being conducted in several countries, globally to exploit vitamin D in the treatment, prevention and reduction of mortality by SARS-CoV-2 infection, but the results are awaited.

d. Other minerals: Copper, iron and selenium

Other mineral under study are iron, selenium and copper. Although copper was proposed for its anti-microbial properties to be used in vessels or as surface to avoid the spread of infection. The other mineral significantly studies is iron, since it is believed that iron helps the SARS-CoV-2 in replication within cell since iron participates in fundamentally important biological processes of DNA/RNA synthesis and ATP generation [72]. Previous studies suggest that iron overload increase mortality in HIV patients, therefore to end HIV viral replication and transcription various iron chelators were used 2-hydroxy-1-naphthylaldehyde benzoyl hydrazine (311) and ICL670 (also known as deferasirox or exjade), 2-benzoylpyridine 4-allyl-3-thiosemicarbazone (Bp4aT) and 2-benzoylpyridine 4- ethyl-3-thiosemicarbazone (Bp4eT), and PPYeT and PPYaT [73-75]. Similarly, it was proposed to treat and prevent SARS-CoV-2 by two ways: one, reduction of free iron ions and iron bound to protein by using strong affinity iron chelators like deferoxamine (DFO, Desferal®), deferiprone (DFP,

Ferriprox®), and deferasirox (ICL670, Exjade®), as proposed by FDA, US; secondly, to reduce it at the cellular level by modulating gene expression involved in iron metabolism [76-78]. The later way of reducing iron need a lot much to explore and research upon, but the iron chelators could be used a promising adjuvant therapy as iron seems to play crucial roles in both host and pathogen. Further, selenium has been proposed to be used in optimum amount as explained by a Chinese study using U-shaped curve; its slight excess as well as deficiency may affect the oxygen and free radical balance in the body [79].

4. SIDE-EFFECTS BY DRUGS AND NUTRIENTS

Therefore, understanding the current scenario we can summarize that there is no current target therapeutic treatment strategy against SARS-CoV-2, but we still hope to get better results by using the drugs and therapies in combination to cure it.

Truly said "Prevention is better than cure", implies that although drugs and therapy may cure the COVID-19, but our daily intake of nutrients enriched diets can prevent us by strong immune system. The macro-nutrients like carbohydrates, proteins and fats play an essential role in providing energy, immune-modulation via amino acids such as arginine, glutamine and sulfur-containing amino acids and influence immune cell function by omega-3 and fatty acid, respectively. The Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) predominantly promote anti-inflammatory and pro-inflammatory effect; they were suggested as novel anti-viral drugs against COVID-19. The micro-nutrients like zinc, vitamin C and vitamin D are undergoing clinical trial phases along with the drugs, as listed in clinical.gov, which suggest that due to their anti-viral properties and potential to modulate inflammatory signals and immune system they can be likely to prevent the COVID-19. Also iron chelators may be considered as potential treatment against COVID-19, as they can reduce the iron load thus enabling the reduction in viral replication and protein synthesis.

5. CONCLUSION

With the present scenario of rapidly spreading SARS-CoV-2 exposure, the big picture ahead is the targeted treatment to cure it, while preventing it. The vaccines and drug development has rapidly begun due to the significant progress of complete genome sequencing of SARS-CoV-2, allowing us to produce accurate, quick and safe diagnostic tools. Its genome sequencing also aided in determining it similarity with SARS-CoV which enabled us to ponder over the pre-used anti-viral drugs and immune-boosters and-modulators.

Summarizing today's scenario, the combined use of drugs and micronutrients has developed a new ray of hope in giving better treatment to patients thus increasing the recovery rate compared with the mortality rate. Together with pharmaceutical drugs and supplemented micronutrients, the pharmaceutical companies and researchers globally have announced the development of vaccines. The vaccines are rapidly undergoing clinical trials to verify their

efficacy and safety, further to reach public domain to put an end to this catastrophic situation. This recombinant biological disaster has not only affected the public health but also caused an imbalance in the global economy of manufacturing supply chains and market demand further affecting infinite sectors linked to it. Therefore it is the need of hour for various institutions, academics, governments, and pharmaceutical companies to join hands to curb COVID-19 and take such preventive measures and future plans to block zoonotic originated potential outspreads.

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7. CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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