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REVIEW



Evaluation of SARS-CoV-2 with a biophysical perspective

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ABSTRACT

This paper intends to contribute to the collaborative efforts of the scientific community by providing a literature review of the status of the coronavirus research by adding a multi-disciplinary perspective and looking into a broad spectrum of SARS-CoV-2 studies on virus molecular structure, biophysical approach, electrostatic interaction and UVC rays. The paper identifies future research directions for each group of studies and points out remaining questions on the way related to COVID-19. The summary of the literature review will intend to assist future studies; provide a biophysical understanding of the virus interaction with host cells and help better identify antiviral therapy and the development of new vaccines/drugs to tackle COVID-19 and any virus outbreak. In addition to the electrostatic interactions of SARS-CoV-2, this paper also discusses whether UVC rays are a safe alternative to many chemical sterilization methods which are frequently used in our daily life since the beginning of the COVID-19 outbreak and whose health effects are controversial. This article also briefly discusses the relationship of some trace elements with COVID-19 infection. In conclusion, focusing on biophysical mechanisms of virus–cell interactions with a broad perspective has potential to give a different approach to the reader for future treatment methods.

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SARS-CoV-2; biophysical perspective; electrostatic interaction; trace elements; UVC sterilization; COVID-19

Introduction

In December 2019, an epidemic disease caused by a previously unknown Coronavirus, eventually named SARS-CoV-2, was reported in Wuhan, Hubei province of China. SARS-CoV-2 stands for Severe Acute Respiratory Syndrome Coronavirus 2. It is a positive sense single-stranded RNA virus that is contagious in humans and causes severe respiratory syndrome [1]. The World Health Organization announced the disease as 'COVID-19' as 'CO' for 'corona', 'VI' for 'virus', and 'D' for disease. The disease mainly targets the throat and lungs and symptoms range from asymptomatic/mild respiratory infections to pneumonia, trouble breathing, lung failure and death [2]. The virus spreads through close contact and *via* respiratory droplets and small particles produced from coughs, sneezes, talking, singing, etc. [3].

The World Health Organization declared the disease as a Public Health Emergency of International Concern on January 30, 2020 and initiated the WHO R&D Blueprint global strategy for acceleration of R&D activities, effective tests and vaccines during epidemics. The WHO declared the disease pandemic on March

11, 2020 [4]. Based on the Worldometer's COVID-19 data the coronavirus COVID-19 affected all the countries and territories around the world. European Centre for Disease Prevention and Control and Worldometer Statistics reported a total of 43 million cases of COVID-19 worldwide and 1.15 million deaths as of October 25, 2020 [5]. The increasing number of cases and high rates of hospitalization and intensive care unit (ICU) admission all around the world are indicating a serious worldwide epidemiological situation [6].

The spread of the disease also caused serious economic loss in many industries such as manufacturing, travel and transportation, retail, energy and resources, high tech and communications, health care and life sciences, university and colleges and affected the stock market significantly [6]. Global stock indices recorded substantial losses due to the coronavirus pandemic [7].

The global high mortality rate and economic damage to many industries and sectors worldwide necessitate studies to develop effective strategies that will help combat the disease and virus [8]. To produce effective drugs and vaccines more studies and

research are needed that will help to underpin the virus biology, traits and infective agents [2].

Therefore the present paper intends to contribute to the collaborative efforts of the scientific community by providing a review of the molecular understanding of viral protein function and the ongoing studies on biophysical approach to the electrostatic interaction of the virus with host cells, UVC sterilization efficacy, relation between trace elements and COVID-19. A deeper biophysical understanding of the virus interaction with host cells may help better identify antiviral therapy and the development of new vaccines [9].

Methods

The bibliographic search was performed on PubMed, Scopus, Web of Science databases, and Google Scholar until October 2020. 'Electrostatic interaction of COVID 19' or 'Biophysical approach for COVID 19' or 'UVC sterilization in COVID 19' or 'UVC and drug treatment' or 'Trace elements and COVID 19' keywords were used to search the databases stated above. Only articles published in English were considered. The identified studies were screened by title, abstract, and full text. The reference list of the studies discussed in this article was also evaluated to increase the sensitivity and selectivity of most literature that we could not define in the databases. One of the authors of this article made the necessary entries to identify duplicate articles. Later, some articles were excluded after reviewing the titles and summaries. Existing articles were carefully evaluated and relevant studies were selected. Overall, 73 articles that we believe reflect the spirit of this research were identified and the subject was discussed in a wide perspective.

Molecular shape and virus biology

SARS-CoV-2 is a member of the coronavirus family which belongs to the order Nidovirales in the family *Coronaviridae* and the subfamily *Coronavirinae* and the genus *Betacoronavirus* [10, 11]. The virus has a diameter of about 65–125 nm [10]. Based on the genome sequencing and phylogenetic analysis, the coronavirus that causes COVID-19, shows very high genome sequence identities (96%) to coronavirus BatCoV RaTG [12] and high genome sequence identities (80%) to the severe acute respiratory syndrome (SARS-CoV) virus [13].

The virus contains spherical or pleomorphic enveloped particles composed of phospholipids, proteins and some viral glycoproteins. The enveloped virus

comprises a single stranded RNA *genome* associated with a nucleoprotein that contains the genetic material of the virus [10]. The virus contains *spike* shaped glycoprotein sticking out from its surface [14]. SARS-CoV-2 virus uses its crown-like spike proteins in attaching the virus to receptors on host cells to mediate coronavirus entry and take over human cells. The envelope supports glycoprotein projections. These glycoproteins on the surface of SARS-CoV mediate membrane fusion for the virus entry. Once the coronavirus binds to a human cell surface through its spike protein, polyproteins are translated from the RNA genome; the viral RNA is released [15]. The nucleocapsid (N) protein mediates binding to viral RNA to form the ribonucleocapsid and regulate RNA synthesis, and also enters the host cell together with the viral RNA [16]. The multifunctional structural nucleocapsid protein plays a crucial role in the virus life cycle, surrounds viral genomic RNA to form part of the virus structure and interact with RNA in a variety of functions and help with genome packaging, functional conformation and virus assembly in the infected host cell [17]. Viral RNA is replicated, synthesized, mutated and assembled in the host cell and the virus takes over the human cell and creates more copies [15].

How SARS-CoV-2 enters into the host cell

Studies using SARS-CoV-2 S protein pseudovirus system found that human angiotensin converting enzyme 2 (hACE2) is the host cell receptor for mediating infection by SARS-CoV-2. ACE2 cell membrane attachment receptors are known as the main port of entry of the coronavirus to host cells [18]. ACE2 is pervasive in many tissues and organs, especially the heart, vessels, gut, lung, kidney, testis and brain [19, 20]. ACE2 is a trans-membrane type I glycoprotein (mono-carboxypeptidase) enzyme molecule. The viral glycosylated spike protein called 'S' that protrudes outside of the virus binds to the ACE2 molecule which connects the inside of the host cells to the outside *via* the cell membrane. The S protein, with a size of 180–200 kDa [15], is the crucial surface protein that is used to bind to the host cell receptor. The S protein spikes are coated with a protective sugar shield, polysaccharide molecules, to camouflage them, and shield the virus from the host's immune system during entry [21]. The S protein is composed of an ectodomain segment, transmembrane (TM) domain anchored in the viral membrane and a short intracellular C terminal segment. The spike protein ectodomain segment consists of two domains- an extracellular N-terminal S1 subunit and a C-terminal S2 subunit, which both mediate the

coronavirus entry into the host cell [15, 22]. The S1 domain that forms the globular head of the S protein is responsible for binding to the host cell receptors [23], and S2 membrane anchoring protein that forms the stalk of the protein is responsible for binding to the host cell receptor through fusing the envelope of the virus with the host cell membrane [24].

Interactions between the viral spike S protein with the host cell receptors initiate the initial virus attachment onto the host cell [25]. After the binding of the S1 subunit onto the ACE2 receptor on the host cell, the heptad repeat 1 (HR1) and 2 (HR2) components of the S2 subunit interact with each other and become helical [26]. That structural rearrangement of the S protein results in the formation of a six-helix bundle (6-HB) fusion core. The 6-HB core structure plays an important role in the viral membrane fusion process, allowing the virus to get closer towards the host cell membrane for fusion and deliver the N-protein to the host cell [7]. Spike proteins of SARS-CoV-2 are activated by a 492 amino acid type II transmembrane serine protease endothelial cell surface protein known as TMPRSS2 [27]. TMPRSS2 as a host cell factor, located to regulate cell–cell and cell–matrix interactions, is highly critical for the entry of the viral particles and spread of viruses. When the S protein binds to the receptor, TMPRSS2 primes the spike protein on coronavirus and facilitates the virus latching onto the cell surface through binding to ACE2 [18]. TMPRSS2 clears the way for SARS-CoV-2 virus *via* proteolytic split of the ACE2 receptor, and split of coronavirus spike glycoproteins, which activates the glycoprotein for host cell entry. Once the virus fuses with the cell membrane and enters into the host cell, it releases its viral RNA and unloads its genetic material into the host cell hijacking the host ribosomes to produce the viral replicative RNA genomes and assemble the new viral particles [28].

To date much research has been conducted on the molecular biology of the corona virus and its entry into the host cell. All these studies contributed to our understanding of the virus yet more research will be of value on the diversifying potential of the virus molecular structure. We also need to learn why host cell reaction to virus entry may differ (as patients have different severity of disease). We need to learn why some individuals are asymptomatic to the virus entry.

Stability of SARS-CoV-2 in different environments

The persistence of SARS-CoV-2 at different environmental conditions outside its host has been studied

whether environmental survival impacts the effectiveness and spread of the virus [1, 29–33]. Studies report that coronavirus is detected and may well survive in different environmental conditions and on surfaces [1, 29–33]. The findings inform that the virus can also be transferred by touch to the contaminated surfaces [32, 33].

Studies on the stability of SARS-CoV-2 in different environmental conditions suggests possible droplet, aerosol transmission of SARS-CoV-2 [3, 32] and reveal that the virus is highly stable at 4 °C, but sensitive to heat [34]. With the incubation temperature being increased to 70 °C, the time for virus inactivation is reduced to 5 min. SARS-CoV-2 in virus transport medium (final concentration ~6.8 log unit of 50% tissue culture infectious dose [TCID50] per mL) was incubated for up to 14 days and then tested for its infectivity. Findings of some studies on the stability of SARS-CoV-2 on different surfaces indicate that the time of complete decay for the infectious virus is three hours on printing and tissue papers; 2 days on treated wood and cloth; 4 days on treated smooth surfaces, glass and banknote; 7 days on stainless steel and plastic and inner layer of surgical mask [33]. Findings of other studies reporting on the stability of SARS-CoV-2 on different surfaces indicate that the time of complete decay for the infectious virus is 1 day on copper; 2 days on cardboard and 4 days on stainless steel and plastic [30]. Findings of studies on the climatic conditions and the spread of SARS-CoV-2 [1] inform that temperature and humidity can play a role in the transmission of SARS-CoV-2. The infectious virus persists at low temperature and low relative humidity [1, 35, 36]. Studies on the persistence of viruses in droplets and aerosols report that viruses survive in aerosols for 3 h in the form of droplets [37, 38]. Spread from touching surfaces is not thought to be the main way the virus spreads. In sum research findings indicate that coronavirus can stay alive on surfaces and a person may get COVID-19 by touching a contaminated surface. Yet the transmission of the virus from touching surfaces is less risky as it is considered an indirect route of transmission that involves a sequence of events, such as virus survival time on the surface is not expired; the surface needs to be touched; unwashed hands are touched to the face. The transmission of the virus through respiratory droplets has higher risk as it has direct contact with the face, nose, mouth and eyes.

Although current studies help us gain understanding on the transmission of the virus and its stability on different surfaces, to date still there are many unknowns about the transmission of SARS-CoV-2. For instance, we

need more research on the dose of the virus from contaminated surfaces required for infection. We need to learn if there are any other transmission routes. We need to learn the proportion of the characteristics of the people (age, gender, vaccinated, non-vaccinated, asymptomatic etc.) and the direct and indirect transmission of the virus. We need to learn the extent of the virus survival in the infected people who remain asymptomatic and the proportion of truly asymptomatic persons who transmit the virus to others.

The biomolecular science approach

Numerous studies developed various biomolecular science approaches to understand how to combat SARS-CoV-2 [39]. The biomolecular science approach offers an array of possibilities to stop the pandemic, i.e. the design of new vaccines, virus neutralizing antibody production, benefiting from the existing antiviral drugs (e.g. lopinavir, ritonavir and remdesivir), usage of plant-based traditional medicines, usage of stem cells for their therapeutic potential and the design of novel synthetic and innovative therapeutic molecules). Yousefi et al. [39] suggested that different molecular structures targeted to combat the virus, can be categorized in four groups: First, highly glycosylated spike proteins, against which antibodies can be produced to cover the surface of the virus hence preventing it from binding to the cell membrane receptor ACE 2. Lectins also can be used to neutralize the attack of the spike proteins to ACE2 membrane receptors. The Transmembrane serine protease TMPRSS2 can also be targeted to prevent the spike protein from getting its mature form and being activated. Second, the cell membrane receptor (ACE2) can be targeted to block the main entrance of the virus to human cells. Third, interleukin 6 receptor (IL6R) and chemokine receptor CCR5 can be targeted as we know that the abnormal cytokine molecular storm that is led by the coronavirus is responsible for most of the deaths of patients with acute respiratory symptoms. Kevzara, Actemra and Leronlimab are three therapeutic antibodies that target these receptors specifically. Infusion of mesenchymal stem cells can also be useful in reducing the high level of the inflammatory molecules in patients' lungs. Fourth, viral RNA polymerase and viral protease can be targeted by some antivirals such as lopinavir, ritonavir, favipiravir and remdesivir.

Chen et al. [40] proposed developing new methods to combat the novel coronavirus SARS-CoV-2 based on existing findings about SARS-CoV. The protein known as RBD219-N1 is a SARS-CoV receptor-binding

domain (RBD) recombinant protein and was previously found to induce high-level neutralizing antibodies and protective immunity against SARS-CoV (MA15 strain) when administered to mice. Chen et al. [40] proposed that SARS-CoV-2 can be neutralized by convalescent serum from SARS-CoV patients. As far as monoclonal antibodies are concerned, it is understood that within the RBD some of the mAbs bind to the receptor-binding motif (RBM), while others bind to domains outside this region. Findings support the possibility of developing a heterologous SARS-CoV RBD vaccine against COVID-19, since the RBD domain is not reflected in RBM amino acid similarity (59%) in between SARS-CoV and SARS-CoV-2. But still, in the region outside RBM, the high sequence similarity (94%) provides the potential for the conserved neutralization of epitopes between the two viruses [40].

In light of these studies, future research should first be conducted on the application of already existing antiviral drugs, plant-based traditional medicines, and stem cell infusion on SARS-CoV-2 infected patients to find out if the expected benefits can be seen in the treatment process. For this purpose, randomised controlled trials should be carried out to obtain more accurate results. In addition, production of new vaccines and virus neutralizing antibodies to target the proposed viral molecular structures should be focused on next. Moreover, taking into consideration the feasibility of developing a heterologous SARS-CoV RBD vaccine, the possible effectiveness of such a vaccine should also be assessed.

Electrostatic interaction with the host cell

Siber et al. [41] studied some aspects of electrostatic interactions in the context of viruses. The study analyzed electrostatic energies and the corresponding osmotic pressures in single-stranded RNA viruses and double-stranded DNA bacteriophages. These two viruses had essential differences in their free energies due to different spatial distribution of their genome. The viruses benefited from the osmotic pressure between the inside of the virus and the external bathing solution, to trail the differences in their free energies. Siber et al. [41] stated that the electrostatic nature influences the energy of protein-genome packaging significantly. The findings revealed that the (nonspecific) electrostatic interactions that a virus has in between its constituents like proteins and its genome molecule, significantly constrains the size and architecture of viruses. Both the replication error rate of a virus; and the physical interactions conducted by

the nucleic acid molecule – which is packed with proteins it encodes – limits the genome length. The study concludes that a functional virus must control and regulate properly the interaction between the evolutionary and physical/structural aspects of the information encoded in its genome molecule [41].

Song et al. [42] studied the crystal structure of a C-terminal fragment of Zika Virus (ZIKV) nonstructural protein 1 (NS1), a major host-interaction molecule that has critical roles in flaviviral replication, pathogenesis and immune evasion, and pointed to its different characteristics at host-interaction interfaces when compared with West Nile (WNV) and dengue virus (DENV) NS1 structures. This difference may indicate that the flavivirus pathogenesis modes differ among these three flaviviruses. The study found that ZIKV may have altered binding properties of host factors and known protective antibodies to flavivirus NS1 due to ZIKV NS1 displaying a loop-surface interface with divergent electrostatic potential [42]. Findings have several implications for future studies. It is suggested that future vaccine development can benefit from eliciting antibodies. Future studies should be focused on the unique surface electrostatic potentials in the three known flavivirus NS1 structures (for DENV, WNV, and ZIKV) to gain a new direction to study more NS1 structures of members of the flavivirus family with various clinical outcomes. To develop new diagnostic techniques for ZIKV infection, the unique surface characteristics of ZIKV NS1 can be helpful. Future studies can also underpin the role that NS1 plays in flavivirus pathogenesis.

Redman et al. [43] studied the filtration and surface charge of recombinant Norwalk virus (rNV) particles. The study demonstrated that pore water pH has a strong influence on the rNV particles' surface charge and filtration in packed beds of quartz sand, over the environmentally important range of pH 5–7. Findings suggested that the physicochemical filtration of the Norwalk virus is highly dependent on the nature and magnitude of electrostatic interactions that develop between the virus and filter media and ZIKV.

Voorthuizen et al. [44] investigated the importance of the absorption characteristics of viruses and the suspending conditions in retention of enteric viruses by MF (microfiltration) membranes. As an alternative way to the sieving of viruses by membranes, few studies have focused on removal of human enteric viruses from wastewater by aggregation and the role of electrostatic and hydrophobic interactions. Voorthuizen et al. [44] used hydrophobic (GVHP) and hydrophilic (GVWP) 0.22 μm MF membranes at different pH levels

and with different salts to investigate the retention of bacteriophage MS-2. As a result, in the presence of salts and with a hydrophobic membrane they measured high retention levels at the iso-electric point of MS-2, pH 3.9 (5 log retention) and pH 7 (4.3 log retention). The hydrophobic membrane's domination of virus retention was clear when compared with a hydrophilic membrane. The salt also improved the retention capacity of the membrane by a proposed mechanism of reduction of the Gouy double-layer when MS-2 was charged (pH 7).

Li [45] reported a comprehensive set of electrostatic features of currently available COVID-19 coronavirus-related structures inside Protein Data Bank (PDB). The PDB ID and structure title of the four COVID-19 Coronavirus-related structures inside PDB respectively are: 6LU7 -The crystal structure of covid-19 main protease in complex with an inhibitor n3; 6LVN - Structure of the 2019-nCoV HR2 domain; 6LXT - Structure of post fusion core of 2019-nCoV S2 subunit; 6VSB - Prefusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up. Li's study was helpful to deepen our understanding of COVID-19's structure and function. The study may have implications for the future outbreaks of the COVID-19 diseases, machine learning and structure-based computational design of neutralizing antibodies or small molecules.

Michen et al. [46] pointed out that the electrostatic charge influences a soft particle's mobility in the electrical and then regulates its colloidal behavior, which plays a major role in the processes of virus sorption. The surface charge of the viruses is pH-dependent in polar media like water. Isoelectric point (abbreviations: IEP or pI) is the pH value at which the net surface charge shifts its sign. The IEP measurements of viruses replicating in hosts of kingdom plantae, bacteria, and animalia are analyzed by them. Virus IEPs turned out to be present in the pH range from 1AE9 to 8AE4; they are most frequently measured in a band of $3\text{AE}5 < \text{IEP} < 7$.

Duval et al. [47] suggested that some widely known and used models and techniques are inadequate to address hydrodynamic and electrostatic properties of microbes (i.e. yeast cells, bacteria and viruses). Electrokinetic phenomena (e.g. electrophoresis), for instance, are helpful in determining the interfacial (double layer) properties of colloidal particles. The theoretical formalisms used to interpret electrokinetic data were originally derived for the restrictive case of hard particles with electrokinetic potential as an inevitable primary variable. Duval et al. [47] suggested that

the zeta-potential principle must be abandoned in examining bioparticles such as bacteria, viruses or yeast cells; since they are characterized by heterogeneous, soft, permeable interphases formed with the outer electrolytic medium, thus requires advanced electrokinetic analyses. To study direct correlation between complex interphase properties of microbes and, their tendency to adhere onto charged surfaces; it is necessary to use appropriate electrokinetics along with other physico-chemical measurements (e.g. AFM imaging/force spectroscopy) and microbiological techniques (genetic manipulation of microbes).

Lai [48] reviewed studies on how the exposure to static and extremely low frequency (ELF) electromagnetic fields (EMF), leads to changes in cellular free radical activities. These studies are in common that EMF exposure can cause changes in cellular reactive oxygen (ROS)/nitrogen (RNS) levels and endogenous antioxidant enzymes and compounds that maintain physiological free radical concentrations in cells. These EMF-induced changes in free radicals can have a significant impact on cell proliferation and differentiation. For instance, through the production of the extremely cytotoxic hydroxyl free radical by the Fenton Reaction, cellular processes can be associated in selective killing of cancer cells. It is known that in several essential survival functions, such as foraging, migration, and reproduction, static- and ELF-EMF signals are used.

Sobsey et al. [49] investigated poliovirus recovery from tap water *via* Microporous filters. Microporous filters are more electropositive than the negatively charged filters, currently used for virus concentration from water by filter adsorption- elution methods. They analyzed the absorption quality of ZetaPlus filters that are composed of diatomaceous earth-cellulose- 'charge-modified' resin mixtures and having a net positive charge of up to pH 5 to 6. The filters performed well by efficiently adsorbing poliovirus from tap water at ambient pH levels 7.0 to 7.5 with no added multi-valent cation salts. Recoveries with Zeta Plus filters averaged 64 percent and 22.5 percent for single- and two-stage concentration procedures, respectively, under water quality conditions where poliovirus recoveries from large volumes of water were less than 5 percent with traditional negatively charged filters and standard methods. Sobsey et al. [49] concluded that electropositive filters had more advantages for concentrating viruses from water than traditional negatively charged filters. Electropositive filters confirm the significance of electrostatic forces in virus recovery from water through microporous filter absorption-elution techniques.

To the present day, there have been many studies conducted to find out more about the electrostatic interaction of various viruses with both the host cell and the environment. Currently, we now have a greater knowledge on how to better clean our waters of microbes, how to develop more effective vaccines to prevent viral diseases, and also by targeting certain mechanisms, we can help already infected people recover faster. To be more successful in combating the COVID-19 pandemic, future research should focus on filtration and the absorption characteristics of SARS-CoV-2; specifically how the electrostatic interactions affect the physicochemical filtration of the virus and specific membrane characteristics that would render virus retention highly efficient. For the vaccine development, the scientific community can benefit from the molecular similarities between SARS-CoV-2 and the coronaviruses SARS-CoV and MERS-CoV, which are responsible for the previous coronavirus outbreaks. Studies have already been conducted to gather information about the molecular structures of these viruses. As EMF is already being used to induce selective killing of cancer cells, a similar kind of method can also be investigated in future research. Changing cellular free-radical and endogenous antioxidant concentrations can make a contribution in the treatment of COVID-19 patients. A summary of the results of the study on electrostatic interactions is presented in Table 1.

Biophysical approach

A biophysical approach to characterizing the virus can be done with Nuclear Magnetic Resonance (NMR) and crystallography. These biophysical methods provide high-resolution data, but they unfortunately require large amounts of material. Studies have shown that these methods are useful when smaller domains of large RNA molecules are studied. The biophysical approach is beneficial in offsetting experimental and financial limitations. Structural probing can aid in defining those smaller domains. Structural probing in combination with phylogenetic studies can provide the basis for two- and three-dimensional models. The models will aid in the selection of the subdomains. Phylogenetic comparisons and thermodynamic calculations create secondary structure models. The thermodynamic stability of RNA structures can be measured by methods such as UV melting or isothermal calorimetry. These methods are measured in dependence on metal-ion concentration. Measuring the observed rate of ribozyme catalysis in dependence on metal-ion concentration is also another option [50].

Table 1. A summary of studies on the electrostatic interaction with the host cell.

Topic	Methods	Results	Conclusion	References
Electrostatic energies and the corresponding osmotic pressures in ssRNA viruses and dsDNA bacteriophages	–	The electrostatic interactions between viral proteins and genome molecule significantly constrain the size and architecture of viruses	Both the replication error rate of a virus; and the physical interactions conducted by the genome molecule limits the genome length.	Siber et al. [41]
C-terminal fragment of Zika Virus (ZIKV) nonstructural protein 1 (NS1): its crystal structure; and differences when compared with West Nile (WNV) and dengue virus (DENV) NS1 structures	–	ZIKV may have altered binding properties of host factors and antibodies to flavivirus NS1 due to ZIKV NS1 displaying a loop-surface interface with divergent electrostatic potential	Future vaccine development can benefit from eliciting antibodies against ZIKV NS1	Song et al. [42]
The filtration and surface charge of recombinant Norwalk virus (rNV) particles	–	Pore water pH has a strong influence on the rNV particles' surface charge and filtration in packed beds of quartz sand, over the range of pH 5-7	Electrostatic interactions between the virus and filter media has a great impact on the physicochemical filtration of rNV	Redman et al. [43]
The importance of the absorption characteristics of viruses and the suspending conditions in retention of enteric viruses by MF membranes	Hydrophobic (GVHP) and hydrophilic (GVWP) 0.22 µm MF membranes were used at different pH levels and with different salts to investigate the retention of bacteriophage MS-2	High retention levels at the iso-electric point of MS-2, pH 3.9 (5 log retention) and pH 7 (4.3 log retention) in the presence of salts and with a hydrophobic membrane	The hydrophobic membrane is superior to a hydrophilic membrane in virus retention. The salt also improves the retention capacity of the membrane.	Voorthuizen et al. [44]
Electrostatic features of currently available COVID-19 coronavirus-related structures	Protein Data Bank (PDB) was scanned	Four COVID-19 Coronavirus-related structures: 6LU7 - The crystal structure of COVID-19 main protease; 6LVN - Structure of the 2019-nCoV HR2 domain; 6LXT - Structure of post fusion core of 2019-nCoV S2 subunit; 6VSB - Prefusion 2019-nCoV spike glycoprotein	SARS-CoV-2 structure and function are better understood	Li et al. [45]
IEP of viruses replicating in hosts of Kingdom Plantae, Bacteria, and Animalia	–	Virus IEPs are in the pH range from 1.9 to 8.4; they are most frequently measured in a band of $3.5 < \text{IEP} < 7$		Michen et al. [46]
Novel models and techniques to address hydrodynamic and electrostatic properties of microbes	–	The zeta-potential principle is not ideal for examining bioparticles such as bacteria, viruses or yeast cells.	It is necessary to use appropriate electrokinetics along with other physico-chemical measurements and microbiological techniques while studying direct correlation between complex interphase properties of microbes and, their tendency to adhere onto charged surfaces	Duval et al. [47]
The impact of static and ELF EMFs on cellular free radical activities	–	EMF exposure can cause changes in cellular ROS/RNS levels, and endogenous antioxidant enzymes and compounds that maintain physiological free radical concentrations in cells	EMF can have a significant impact on cell proliferation and differentiation by inducing changes in free radicals	Lai [48]
Poliovirus recovery from tap water via Microporous filters	Analysis of ZetaPlus filters that are composed of diatomaceous earth-cellulose-'charge-modified' resin mixtures and having a net positive charge of up to pH 5 to 6	Recoveries with Zeta Plus filters averaged %64 and %22.5 for single- and two-stage concentration procedures, respectively, under water quality conditions where poliovirus recoveries from large volumes of water were less than %5 with traditional negatively charged filters and standard methods	Electropositive filters have more advantages for concentrating viruses from water than traditional negatively charged filters	Sobsey et al. [49]

Biophysical characterization

Jourdan et al. [51] investigated the biophysical characteristics of the nucleocapsid (N) protein from a highly virulent North American strain of porcine reproductive

and respiratory syndrome virus (PRRSV). The arterivirus N protein is a multifunctional protein that binds viral RNA for encapsidation and has potential roles in host cell processes. As far as methodology is concerned; the N gene from PRRSV strain NVSL #97-7895 was

cloned into the pTriEx1.1Neo (Novagen) vector. Site-directed mutagenesis helped forming the plasmid pTriExNC23S coding for an N protein carrying a cysteine (cys) to serine mutation at residue 23. In order to achieve efficient protein expression, plasmids coding for N protein variants were transformed into Tuner (DE3) pLacI (Novagen) *Escherichia coli* cells. Then, purified protein samples were analyzed using analytical gel filtration chromatography. Protein standards were used to establish a standard curve; Cytochrome C (12.4 kDa), carbonic anhydrase (20 kDa), bovine serum albumin (66 kDa), α -amylase (200 kDa), catalase (210 kDa), Dextran blue (2000 kDa). Then, the proteins were purified to be used in Circular Dichroism (CD) analysis. CD data were analyzed using Dichroweb [21]. The findings showed that the formation of disulfide bridges played a key role in RNA binding, providing a clarification of why infectious viruses cannot be rescued if cysteine residues are mutated, and that RNA binding can be promoted by multiple sites.

Kettleson et al. [52] employed an Electrostatic precipitator (ESP) to study airborne virus capture and inactivation at applied voltages from -10 to $+10$ kV by making use of aerosolized bacteriophages T3 and MS2. Samples were obtained from the effluent air stream for each charging scenario and assayed for viable phages using plaque assays and for nucleic acids using quantitative polymerase chain reaction (qPCR) assays. It resulted in more virus particles being captured from the air at higher applied voltages, with maximum log reductions of 6.8 and 6.3 for the plaque assay and 4.2 and 3.5 for the qPCR assay of -10 kV for T3 and MS2, respectively. The reason for the log reduction values obtained with the plaque assay being much greater than those obtained with the qPCR assay was that, although present in the effluent (liquid waste), nonviable particles were not accounted for in the plaque assay. When these assays were compared, it was apparent that the highest applied voltages enabled a greater in-flight inactivation (i.e. inactivation without capture) with a log inactivation of 2.6 for both phages at -10 kV given that conditions in the ESP are imposed to produce a corona discharge. Kettleson et al. [52] demonstrated that there is a significant potential for virus capture and inactivation through continual ion and reactive species bombardment.

Based on the already existing literature and his own data, Ayrapetyan [53] demonstrated Na/K pump's role in the metabolic control of semipermeable properties and excitability of neuronal membrane, as well as its auto-regulation induced by cell hydration. As he states, there was a need to lay stress upon this subject, since the conductive membrane theory of

Hodgkin-Huxley-Katz, on which our knowledge about the biophysical properties of cell membrane is based on, had not been satisfactory in elucidating the role of electrogenic Na/K pump in regulation of semipermeable properties of cell membrane, which is primarily due to the fact that the theory is developed on internally perfused squid axon and lacks intracellular metabolism. In summary, Ayrapetyan [53] concluded that: the control of potassium electrode properties predicted by Nernst's law renders the electrogenic Na/K pump to generate metabolic components of membrane potential; the elevation of membrane resistance gives rise to an increase in Na/K pump current, even though it's not the case with ionic gradient-induced membrane currents; the pump maintains the control of the semipermeable properties of cell membrane in resting state of neuron through increasing endogenous water formation by activation of oxidative phosphorylation and generates water efflux from the cells; the Na/K pump activation leads to a reduction in the number of functionally active Na channels in membrane; there is also a negative feedback between cell volume and Na/K pump activity; and finally the curve of dose-dependent ouabain binding with the cell membrane in intact neurons consists of two saturated and one linear component, from which Na/K pump functions are characterized by low affinity receptors with linear dose-dependent character.

As future research, a great effort should be spent on the investigation of how to capture SARS-CoV-2 from the air. This is of great importance, especially when taking the extent of the pandemic into account and how much the air indoors must be contaminated with the viral particles due to the asymptomatic infected individuals. It can be expected to see a reduced number of new cases as the indoor air is cleared of the infectious viral particles. Moreover, the certain molecular mechanism of how SARS-CoV-2 nucleocapsid proteins hold the RNA genome can be identified, and *via* inducing disruptive mutations, the N protein can be rendered dysfunctional to halt the disease progression in infected patients. A summary of the studies on biophysical characterization is presented in Table 2.

Ultraviolet C (UVC) and antimicrobial properties

UV light has known antimicrobial properties. It has been used for years in the water sanitation sector and the food sector. The idea of using UV light for surface decontamination in health care facilities has been recently introduced. UVC is a broad-spectrum

Table 2. A summary of the studies on biophysical characterization.

Topic	Methods	Results	Conclusion	References
The biophysical characteristics of the nucleocapsid protein from a highly virulent North American strain of porcine reproductive and respiratory syndrome virus	Cloning of the N gene into the pTriEx1.1Neo vector. Analytical gel filtration chromatography Protein purification	The formation of disulfide bridges plays a key role in RNA binding	Infectious viruses cannot be rescued if cysteine residues are mutated because the disruptions in RNA binding are caused by defects in the formation of disulfide bridges.	Jourden et al. [51]
Airborne virus capture and inactivation	Use of aerosolized bacteriophages T3 and MS2 –10 to +10 kV voltage Application Samples Plaque assays qPCR assays	More virus particles were captured from the air at higher applied voltages Maximum log reductions of 6.8 and 6.3 for the plaque assay and 4.2 and 3.5 for the qPCR assay of –10 kV for T3 and MS2, respectively.	There is a significant potential for virus capture and inactivation through continual ion and reactive species bombardment.	Kettleson et al. [52]
Na/K pump's autoregulation and its role in metabolic control of semipermeable properties and excitability of neuronal membrane	–	The conductive membrane theory of Hodgkin-Huxley-Katz is not satisfactory in elucidating the role of electrogenic Na/K pump in regulation of semipermeable properties of cell membrane	Na/K pump and the neuronal membrane have enormous roles in regulating each other	Ayrapetyan [53]

antimicrobial agent which can be used to decontaminate equipment and room surfaces. Studies have shown that UVC decontamination has certain drawbacks such that the room must be completely vacated before UVC decontamination commences. Studies have not been able to show the efficacy of UV light in decontaminating shadowed areas of the room or that UV room disinfection has the ability to decrease the rate of healthcare associated infections. Studies have shown H_2O_2 use, an antimicrobial agent, reduced the rate of healthcare-associated infections. Moving items in the room to be disinfected is unnecessary with the use of H_2O_2 . H_2O_2 use does not leave any residue behind [54].

Kowalski et al. [55] used the D90 value (the UV exposure dose required for 90% inactivation) and UV rate constant (the susceptibility of viruses to UV light) to determine an absolute indicator of UV susceptibility in the first stage of decay. The UV rate constant is the slope of the survival curve on a logarithmic scale. By evaluating complete genomes, they created a mathematical model for the ultraviolet susceptibility of microbes. They analyzed the genomes of viruses, bacteriophages, and bacteria using base-counting software to determine the frequencies of potential dimers. The D90 value, which is the average rate constants, was determined by using the UV rate constant data for ssRNA and dsDNA viruses. They correlated UV susceptibility (D90) with the genomic model and produced the R2 values for viruses and bacteria. Their results correlated well with the UV rate constant data available. Their mathematical model may be used to estimate the UV rate constants for a myriad of pathogens for which complete genomes are available [56]. Their model has potential to determine the UV

susceptibility of risky pathogens without the risk of handling them in laboratory tests.

Shen et al. [57] conducted a study on the efficacy of UVC-LED (Ultraviolet light emitting diode) in the disinfection of water. Their study showed that UVC-LED effectively inactivated tetracycline resistant *Bacillus* bacteria in an energy-efficient and resistance-reducing manner. The study used UVC-LED in the range of 200–280 nm to treat the water of gram-positive tetracycline-resistant *Bacillus* bacteria (TRB) and their tetracycline resistant gene (TRG). They found that UVC-LED was effective in inactivating tetracycline resistant bacteria up to 5.7 – log and has the ability to inhibit the tetracycline resistant gene expression. The tetracycline resistant gene expression was particularly inhibited at 268 nm. After UVC-LED irradiation, they found that the regrowth ratio of the TRB was significantly high 24 h after irradiation. However, the number of regrown bacteria in the irradiated water was still lower than the number of bacteria in the non-irradiated water. The amount of fluence required was similar to that of the referential non-resistant bacteria using the same UVC-LED. Post UVC-LED irradiation they found that the mechanism to repair TRB was *via* photoreactivation which is similar to the repair mechanism of non-resistant bacteria.

Elhahidy et al. [58] evaluated the efficacy of ultrafiltration membranes as a virus removal mechanism using two virus surrogates (MS2 and uX174 bacteriophages). Low pressure ultrafiltration membranes are most commonly used in the process of treating drinking water. The membranes filter out microbiological contaminants. In the study they used two virus surrogates with a similar size but different surface characteristics. Though

smaller, they found that the MS2 bacteriophage was removed better. The removal of the uX174 bacteriophage was found to significantly decrease as the pH of the feed solution increased to 9.4 from 6.5. They determined the main removal mechanism to be size exclusion. They also found that electrostatic repulsion was crucial in the additional removal of MS2 above the baseline size exclusion. They found that the difference in the removal patterns between the two bacteriophages could also be attributed to the higher isoelectric point and complex capsid structure of uX174.

Beck et al. [59] conducted a study evaluating the performance of UVC-LED disinfection and investigating potential dual-wavelength synergy. They used a dual wavelength UVC-LED unit, which emits at peaks of 260 nm and 280 nm. They evaluated the combination of 260 and 280 nm together for its inactivation efficacy and energy efficiency in disinfecting various bacteria and viruses such as *E. coli*, human adenovirus type 2, *Bacillus pumilus* spores and MS2 coliphage. They also used the dual-wavelength unit to measure potential synergistic effects of multiple wavelengths on bacterial and viral inactivation. Their results suggested that they must reach efficiencies of 25–39% to match the electrical efficiency per order of log reduction of conventional LP UV sources. They were not able to detect dual wavelength synergies for microbial inactivation.

UVC ultraviolet light has long been established as a method of inactivating airborne pathogens but it has limitations for the widespread use in public settings due to its carcinogenic and cataractogenic effects. Welch et al. [60] suggested Far-UVC light as a possible tool to control the spread of airborne-mediated microbial diseases such as influenza and tuberculosis. Far-UVC light (207–222 nm) can efficiently inactivate bacteria without harming mammalian skin due to its inability to penetrate the outer layers of human skin or eye. Far UVC has the ability to penetrate and inactivate more than 95% of aerosolized H1N1 influenza virus at a very low dose of 2 mJ/cm² of 222 nm light. They suggest the use of constant very low dose rate far UVC light in indoor public locations is a promising and safe method to control the spread of airborne-mediated microbial diseases.

Eickmann et al. [61] used UVC light to inactivate severe acute respiratory syndrome coronavirus (SARS-CoV), Crimean-Congo hemorrhagic fever virus (CCHFV) and Nipah virus (NiV), in platelet concentrates. They used methylene blue plus visible light to inactivate those three emerging viruses in plasma. Those viruses pose a threat to transfusion safety so effective methods of pathogen inactivation is crucial. They spiked the blood products with those viruses, and they

investigated the ability of UVC light and methylene blue plus visible light inactivation systems to inactivate the viruses in the platelet concentrates and plasma. They found that both of the inactivation systems effectively reduced the infectivity of the SARS-CoV, CCHFV and NiV in platelet concentrates and plasma.

Eisenlöffel et al. [62] investigated the efficiency of UVC irradiation with air filtration in reducing airborne microorganisms. They implemented a UVC-combined recirculating air filtration module in a small animal facility, and they assessed its ability to improve the air quality in terms of airborne bacteria and dust. They used aerosols of bacteria such as *Staphylococcus aureus* and viruses such as porcine respiratory virus in their experiment. Their findings suggested that recirculating air filtration combined with UVC (UVC module) efficiently reduced the airborne pathogens in the barn compared to the reference barn. Their research showed that there was an average reduction to 37% of reference values for bacteria and a reduction to 78% of reference values for dust. They measured the value before and after the implementation of the UVC module and they found a reduction of 99.4% for airborne bacteria and 95.0% for total dust.

There has been a shortage of personal protective equipment (PPE) worldwide due to the pandemic. Due to a global PPE shortage the World Health Organization suggested strategies to enable optimal PPE availability. Healthcare facilities have taken to decontaminating N95 respirators for reuse to combat the shortage of PPE available. UVC (ultraviolet C) has been used due to its germicidal properties. Narla et al. [63] stated the significance of the minimum dosage necessary for UVC decontamination of N95 respirators during the COVID-19 pandemic. Presently, the UVC dosages for N95 respirator decontamination varies greatly. There is no published data about the ideal UVC dose needed for the decontamination of the N95 respirators from SARS-CoV-2. There are studies available regarding the other coronaviruses, such as MERS-CoV and SARS-CoV. Heimbuch et al. [64] found that by 1 J/cm² of UV decontamination all six of the viruses (H5N1, H5N, H1N1, H7N9, MERS-CoV, SARS-CoV) were not viable. There was a drawback to the study due to the fact that they only used one type of respirator in the study. Mills et al. [65] and Heimbuch et al. [64] reported the 1 J/cm² dose may not sufficiently decontaminate respirators of different materials and types. It is crucial that at least 1 J/cm² dose be used for UVC decontamination methods to safeguard healthcare workers. Though there are limitations to the UVC decontamination methods, during severe shortages of N95 respirators, it may be used to ensure PPE availability to health-care workers [63].

Table 3. A summary of the studies on UVC and antimicrobial properties.

Topic	Methods	Results	References
UV inactivation rate constant for RNA and DNA viruses	Base counting software	UV susceptibility (D90) was correlated with the genomic model and produced the R2 values for viruses and bacteria.	Kowalksi et al. [55]
UVC-LED in water disinfection on <i>Bacillus</i> species	UVC-LED	268 nm is more effective for TRB and TRG treatment.	Shen et al. [57]
Viral removal by ultrafiltration membranes	Ultrafiltration membranes	MS2 bacteriophage was removed better. uX174 bacteriophage removal decreased as the pH of the feed solution increased	Elhadidy et al. [58]
UV-C LED disinfection and potential dual-wavelength synergy	Dual wavelength UVC-LED unit	Must reach efficiencies of 25–39% to match the electrical efficiency per order of log reduction of conventional LP UV sources. Unable to detect dual wavelength synergies for microbial inactivation.	Beck et al. [59]
Far-UVC light to control the spread of airborne-mediated microbial diseases	Far-UVC light	Far UVC can inactivate more than 95% of aerosolized H1N1 influenza virus at a very low dose of 2 mJ/cm ² of 222 nm light.	Welch et al. [60]
Inactivation of 3 emerging viruses (SARS-CoV, CCHFV, NiV)	UVC light for viruses in platelet concentrates Methylene blue plus visible light for viruses in plasma	Both inactivation systems effectively reduced the infectivity of the viruses	Eickmann et al. [61]
Efficiency of UVC irradiation with air filtration in reducing airborne microorganism	UVC-sustained recirculating air filtration	Recirculating air filtration combined with UVC efficiently reduced the airborne pathogens in the barn compared to the reference barn.	Eisenlöffel et al. [62]
UV decontamination of H5N1, H5N, H1N1, H7N9, MERS-CoV, SARS-CoV	UV decontamination	1 J/cm ² for UV decontamination made the viruses non-viable	Heimbuch et al. [64]
UV germicidal irradiation of influenza contaminated N95 respirators	UVGI dose optimization	The minimum UVGI dose for ≥ 3 -log reduction in viable H1N1 influenza was 1 J/cm ²	Mills et al. [65]

Further research on Far-UVC may be beneficial as it is a promising method of efficient decontamination and it is less dangerous for human skin than UVC. Future research comparing the decontamination of Far-UVC with conventional germicidal UVC is necessary as few studies on this topic currently exist. Research on the effects of UV-C and Far-UVC on various parts of the human body such as the nerves and bones may prove beneficial in determining the safety of these methods. Furthermore, methods to attenuate the harmful effects of UVC should be studied. A summary of the studies on UVC and antimicrobial properties is presented in Table 3.

Trace elements and COVID-19

As it is known, zinc has important roles in antiviral activity; selenium is a free-radical scavenger and supports cellular immunity; iron is needed for some reactions and cellular functions such as RNA/DNA synthesis and repairs; magnesium has important roles in immune functions; copper is an essential trace element in the body and necessary to protect DNA from oxidative stress; sodium can regulate immune cell activities; potassium is important for cell functions and the need for membrane potential; calcium plays a role in the activation of lymphocytes (reviewed in [66]). It has been reported that there is some relationship between the trace elements, ions discussed here,

and COVID-19. Zinc inhibits the activity of RNA-dependent RNA polymerase of coronavirus, and therefore compounds both of zinc and CQ/HCQ could be useful for COVID-19 treatment. High selenium intake causes better and more immune responses. High levels of iron may increase viral infections, although it has been reported that COVID-19 patients have low serum levels of iron. Reportedly, copper deficiency can reduce the human immune system response. However, the serum copper level in COVID-19 patients is still unknown. The sodium in patients with pneumonia infected by SARS-CoV-2 is lower than that in non-pneumonia patients. Hypokalemia is a high prevalence condition among COVID-19 patients. It has been also reported that SARS-CoV entry into some cell lines decreases when intracellular calcium decreases [66]. The pooled analysis performed by Lippi et al. [67] indicated that COVID-19 severity is associated with lower serum concentrations of sodium, potassium and calcium. It was later indicated that 93% of acute and seriously ill patients with COVID-19 have hypokalemia and hypokalemia is a widespread outcome in cases with hypomagnesemia [68]. Chams et al. [69] stated that zinc in combination with zinc-ionophores like pyrithione inhibited the replication of SARS-CoV in cell cultures. Therefore, zinc supplementation may be of potential benefit for prophylaxis and treatment of COVID-19 and it is currently under investigation in multiple clinical trials in combination with other

Table 4. A summary of the articles focused on relation between trace element and SARS-CoV-2.

	Zinc	Selenium	Iron	Copper	Na	K	Ca	Mg
Taheri et al. [66]	Zinc inhibits the activity of RNA-dependent RNA polymerase of coronavirus, and therefore compound both of zinc and CQ/HCQ could be useful for COVID-19 treatment	High selenium intake causes better and more immune responses	High level of iron may increase viral infections, although it has reported that COVID-19 patients have low serum level of iron	Copper deficiency can reduce human immune system response. However, serum copper in COVID-19 patients is still unknown	Sodium in patients with pneumonia infected by SARS-CoV-2 is lower than in non-pneumonia patients	Hypokalemia is a high prevalence condition among COVID-19 patients	SARS-CoV entry into some cell lines decreases when intracellular calcium decreases	
Lippi et al. [67]					Lower serum concentrations of sodium	Lower serum concentrations of potassium. 93% of acute and seriously ill patients with COVID-19 have hypokalemia and hypokalemia is a widespread outcome in cases with hypomagnesemia		
Chams et al. [69]	Zinc supplementation may be of potential benefit for prophylaxis and treatment of COVID-19							
Rahman and Idid [70]	Zinc supplementation could play an important role to treat COVID-19 patients							
Hiffler and Rakatoambinina [71]		Selenium might reduce the effect of SARS-CoV-2 on vascular endothelial cells and aggregation of platelets						Magnesium supplementation is expected to play an active role in clinical practice in the prevention and treatment of COVID-19
Tang et al. [72]								
Zhang et al. [73]		Redox-active selenium species formed from high selenium intake might hypothetically inhibit SARS-CoV-2 proteases						

agents including hydroxychloroquine, vitamin C and vitamin D. Rahman and Idid [70] stated that Zinc supplementation could play an important role to treat COVID-19 patients such as added immune-boosting effects with anti-viral drugs and stopping SARS-CoV-2 replication in infected cells if combined with chloroquine. Hiffler and Rakatoambinina [71] suggested that selenium might reduce the effect of SARS-CoV-2 on vascular endothelial cells and aggregation of platelets. Tang et al. [72] summarized that magnesium supplementation is expected to play an active role in clinical practice in the prevention and treatment of COVID-19. Zhang et al. [73] commented on the fact that the synthetic redox-active selenium compound, ebselen, has been found experimentally to be a strong inhibitor of the main SARS-CoV-2 protease that enables viral maturation within the host. That finding suggests that redox-active selenium species formed from high selenium intake might hypothetically inhibit SARS-CoV-2 proteases. They consider the tactics that SARS-CoV-2 could employ to evade an adequate host response by interfering with the human selenoprotein system. Recognition of the myriad of mechanisms by which selenium might potentially benefit COVID-19 patients provides a rationale for randomized, controlled trials of selenium supplementation in SARS-CoV-2 infection. The relationship between trace elements and SARS-CoV-2 infection is a very broad topic. Therefore, examining this relationship is the subject of a different paper or papers. However, the purpose of discussing trace elements in this review is only to give a very brief summary of recent studies on the relation between some trace elements and COVID-19. In other words, our aim is to make a small contribution to researchers who aim to focus on these issues in the future. Finally, the additional intake of microelements should take place after an established deficiency. In general, the impact on the immune system in general and in infection with SARS-CoV-2 is a delicate topic, because we expect from the immune system to be not 'strong' but adequate. A summary of the articles focused on relation between trace element and SARS-CoV-2 is presented in Table 4.

Conclusions

In this paper we intend to provide a summary of the status of COVID-19 research by adding a multi-disciplinary perspective and looking into a broad spectrum of studies on the molecular understanding of the viral protein function, biophysical approach, electrostatic interaction of the virus with host cells, relation between trace elements and COVID-19, UV interaction with viruses and drugs. The paper highlights some findings

of the current research on COVID-19 and identifies some remaining questions for future research for each group of studies. To date there are still many unanswered questions and many unknowns on the way that relate to COVID-19. Therefore raising questions for future research will be of value. Hopefully the literature summary included in the present review would be useful for future research to combat COVID-19 and any virus outbreak and may help identify anti-viral therapy and the development of new vaccines and provide more robust recommendations to manage COVID-19. As a result, focusing on biophysical mechanisms of virus–cell interactions with a broad perspective can be seminal for future treatment methods.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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