Opportunities and mitigation strategies for biomaterials: to combat the challenges of COVID-19 outbreak

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Abstract. In the last several months, “Coronavirus Disease 2019” (COVID-19) has intensified to a global pandemic at an abnormal rate. This pandemic of COVID-19 has disclosed major flaws in our abilities to attenuate spreading of contagious viral disease providing treatment for patients, leading to crisis in public health. Various Clinical views are discussed, considering the mitigation tactics and scope for novel biomaterials involved in treatment strategies, diagnostics and surface coatings for deactivation of virus. Call for multidisciplinary approaches in disease detection and management by biomaterials community are expected to play a vital role to combat the challenges of present and future outbreaks.

Keywords: Antiviral, Biomaterials, Pandemic, Diagnostics

1. Introduction
With the advancement in vaccination, antibacterial development alongside with public hygiene, humanity is far less susceptible to any type of infectious diseases. In the last several months, “Coronavirus Disease 2019” (COVID-19) has intensified to a pandemic globally at an abnormal extent. Recognised as a novel beta-coronavirus having similarity with other zoonotic SARS-coronaviruses, the suspicion is made that SARS-CoV-2 invaded into human populations from bat host by way of a wet-market located in Wuhan City, China [1]. It has abruptly diffused to almost every corner in the world. This pandemic of COVID-19 has disclosed several flaws in our abilities to attenuate spreading of contagious viral disease and furnish medical treatment to patients, leading to a crisis in public health [2]. A cursory search on PubMed reflects that higher level of researches has been performed by the biomaterial community focusing on antibacterial work due to the fact that 90 articles were having the keywords “biomaterial and antiviral” but for the same search with “antibacterial and biomaterial” more than 3,500 results in the last 5 years as of May 2020. In order to promote rapid solving of problems and progress scientifically during this pandemic, our goal is to explore the present clinical practices against corona virus and how research work on biomaterials can furnish in current and future pandemics.

2. Challenges
The virus named SARS-CoV-2 was spotted first in December 2019 in Wuhan city located in China in the form of cluster of pneumonias [3]. From that moment onward, it is seen that this virus has spreaded globally at an alarming rate and hasaffected the human community at a larger extent and is expected to cause fatal infections and lakhs of deaths in the upcoming days [4]. Some interesting insights we get when we briefly compare SARS-CoV-2 with viruses MERS coronavirus and SARS
coronavirus. Even though all the three viruses are transmitted zoonotically, but COVID-19 remarkably characterises itself from others by – how widespread and rapidly it can outspread, its rate of mortality rate is low if comparison is done to the other two viruses [5,6].

2.1. Transmission Mechanism of SARS CoV-2 and infection

Basically, the main way for transmission of a zoonotic virus is human-to-human through droplets, fomites and close contact[7]. But it becomes a matter of great concern when – a patient who had been exposed to the virus for a weeks before the onset of symptoms (asymptomatic carrier) [8]. Moreover, the evidence for the growth of SARS-CoV-2 for its highly infectious nature is due to its potential to move in aerosols that are recognised widely as smaller respirable droplets having diameter ranging <5-10μm with its capability of long-range airborne transmission [9,10]. In the Journal of the American Medical Association, a brief classification on patients has been done by the Center for Disease Control on the basis of symptoms into:

- mild (81%),
- critical (14%),
- life-threatening infection (5%) category [11].

Major Symptoms that have been observed for those critically life-threatening infected people are headache, cough for little infection and gastroenteritis, sepsis and multi-organ dysfunction (MOD), ventilator-dependent respiratory failure [3,12].

2.2. Indicators for Mitigation Effectiveness of COVID-19 and Pandemic Severity

Most countries generally tried different strategical approaches and waited for the results. The response plan of action gets changed with time if considered in the duration prior to the peak of the pandemic and achieving stability after attaining the peak. At the early stage, the mitigation effectiveness \( E_e \) is calculated by time consumed for reaching the peak and at the latter phase, mitigation effectiveness \( E_f \) is evaluated by the maximum rate of drop during the point of final observation and peak. A diagram can be sketched based on \( E_e \) and \( E_f \) for determining the overall mitigation effectiveness \( E_o \) where the delimiters \( o, e \) and \( f \) resembles the whole period, early stage and later stage. Severity of pandemic \( S_i \) is calculated as the ratio of total number of confirmed cases \( N \) to population \( P \) for each day, expressed as:

\[
S_i = \frac{N_i}{P_t} \quad \text{(1)}
\]

Here, \( t \) signifies number of days spent at the early stage \( (i = e) \), the latter stage \( (i = f) \), or the total period \( (i = o) \). The mortality rate for the entire time period denoted as \( d \) is also assigned for getting the measure for severity of pandemic, measured by the ratio of total number of deaths \( D \) to population \( P \) per day, revealed as:

\[
d = \frac{D}{P_t} \quad \text{(2)}
\]

where \( t \) denotes the number of days that covers the entire time period [13].

3. Mitigation Strategies

After the outburst of COVID-19, the advent of SARS-CoV-2 has become one of the salient focus areas in the field of biomaterials research. A brief outline of present clinical standards is shown and following which current opportunities for intervention of biomaterials are also discussed in the following sections.

3.1. Diagnostic techniques

The emergence of Reverse Transcription Polymerase Chain Reaction (RT-PCR) for nucleic acid testing has paved the way as the most typical means to screen samples for patients having infection of SARS-CoV-2 that has been outbroken globally [12,14]. Subsequently, the outburst of COVID-19 has led the international collaboration to the rapid advancements of detection kits for SARS-CoV-2 based on RT-PCR which is recognised as a major worldwide achievement.
3.1.1. Point-Of-Care Nucleic Acid Testing. Several limitations are faced in RT-PCR testing for the contemporary SARS-CoV-2 in:

- collection of sample and stages of processing,
- several congestions in testing workflow,
- Lack of PCR instrument infrastructure which led to the inadequate access to testing in those areas.

Thus, strategies of point-of-care (POC) have emerged as alternative domain of research in present-days. Preferably, POC tests provide diagnoses without any requirement of laboratory by virtue of off-site means for sample processing and its results leads to the elimination of the exigency for specialized instruments, permitting tests to be performed in the field or even at home as well. The advantages of this process are: i) During centralized testing and processing, the risk of spread of the disease gets reduced. ii) Testing throughput and capacity can be increased. iii) In the less/under developed areas where the income limit of people is low, access to more testing can be possible. Biomaterial’s laboratories can assist in the fabrication of key disposables comprising of test swabs for collecting samples. For example, Formlabs has designed and approved nasal swabs that are being 3D printed for collecting respiratory specimens [15]. Biomaterials also plays a vital role for the formulation of the point-of-care tests. Emergence of these POC nucleic acid tests combining with synthetic as well as modern molecular biology inventions with advanced biomaterials progresses to simplify detection of disease in low technology [14].

3.1.2. Application of Isothermal RT-PCR Tests. Biomaterial researchers can provide important technological advancements facilitating development of next-generation diagnostic tests. In [16], the development of a system that is magnetic nanoparticle-based is shown, that performed DNA and RNA isolation quickly from samples after a magnetic field is applied to help in nucleic acid purification. A chemiluminescent reporter system based on magnetic nanoparticle, has also been illustrated for the detecting target sequences with a comparatively simple instrument. Biomaterials allow for the elucidation of assay results on the basis of colorimetric analysis without any use of specialized optics, thus make them a prototype for detection by virtue of POC. According to aggregation property, surface chemistry, size, shape, the biomaterials-based surface plasmon resonance biosensors for example, quantum dots or gold nanoparticles are illustrated for changing colour thus producing them excellent optical probes [17, 18]. It can be manipulated for the production of simple colorimetric readouts by virtue of complex molecular reactions. Efforts for applying this technology (and other alike ones) for the development of COVID-19 tests are on the way [3,19]. Specific High-sensitivity Enzymatic Reporter unlocking, popularly known as SHERLOCK - a novel nucleic acid test, has obtained authorization from US Food and Drug Administration Emergency Use Authorization for detection of COVID-19 in the clinical specimens. For doing test in a single step of clinical samples, reagents of the test (which includes ribosomes, enzymes-buffers, substrates) can be lyophilized in a disc of single paper. Moreover, this platform has been proved to be highly economical and also excelled enlarging access for testing for lesser instrument requirement. To confer this technological advancement for COVID-19 patients, the work is underway [12,20].

3.1.3. Use of Nucleic Acid Biosensors. A day will come when emergence of biosensors with extremely detection capability of low limits, may lead for simpler as well as faster one-step detection, which would help for eradication of cDNA amplification phase as well as reverse transcription step completely. A large number of nucleic acid biosensors and transducers are found which includes nanostructures having surface-functionality and DNA-responsive smart materials with programmable features [21, 22]. Nanoislands become functional with complimentary DNA that allows for encapsulation of targeted RNA. Detection of variation in localized surface plasmon resonance can be observed in retaliation to binding of RNA. For enhancing the sensor technology that are existing, biomaterials strategies can be implemented. To escalate this amplification of signal by reducing the requirement for amplification of cDNA, the development of a cationic copolymer has been explained in [23], which facilitated in the
assemblage of MNAzymes, enhancing the catalytic potentiality of the enzyme dramatically for yielding a 200 times faster rate for the conversion of substrate to distinguishable product.

3.1.4. Viral Antigen Testing. Nucleic acid testing is the prevalent method for the diagnosis for the patients affected by COVID-19. But, designing of biomaterials can pave the way in the detection of viral antigens present on the surface of an undamaged virus. These types of diagnostics are proved to be extremely beneficial, as – (i) They require either low or no sample pre-processing that can instantaneously sense the viral existence in complex biological systems specially in case of fluids. (ii) Extremely low detection limits are required to afford relevance of clinical purpose without any amplification involvement. In addition, with the decrease in the detection limits, the selectivity of pathogen is utmost and to maintain excellent specifications. Biosensors such as electrochemical or optical biosensors, piezoelectric for the detecting slight changes in mass, optical features and electrical activity play a vital role in biomaterials research [24-26]. Emerging biomaterial sensors should reveal the ability for surpassing the susceptibility and specification of conventional nucleic acid tests for replacing current standards.

3.2. Therapeutic Facilities

3.2.1. Nanodecoys. Nanostructures are fabricated to mimic living cells, as an alternative of nanomaterials centered strategy, known as nanodecoys. These are produced from or contain derived materials from cell membrane to capture and isolate viruses. Current progress in entry routes used by SARS-CoV-2 could be utilized to trap virus for creating nanoscale cell-mimicking decoys. Particularly, the unification of host cell membranes with SARS-CoV-2 is proceeding by interactions between viral S proteins, proteases and ACE2 like, the transmembrane protein TMPRSS2 [27-29]. Decorating the ACE2 protein or related fragments of protein with cell-mimetic nanoparticles could more furnish biomimetic presentation of the protein.

3.2.2. Extracorporeal Blood Treatment. The employment of extracorporeal blood treatments acting as one of the therapeutic strategies would play a vital role in the mitigation of the severe damaging sides of COVID-19. Extracorporeal membrane oxygenation (ECMO) devices are operated clinically for highly critical ill patients but are found mostly at specialized centers due to the fact that these types of machines are in lesser supply in comparison to that of ventilators and are very cost effective to operate [30,31]. So, as an alternative, emerging micro- as well as nanoparticle carriers of oxygen may develop more hospitable tactics for extracorporeal blood oxygenation [32]. For critically ill patients, oxygenation alone may not be sufficient enough for reducing rate of mortality. A recent analysis in [33] shows that most of the COVID-19 patients died from multi-organ failure or septic shock when treated with ECMO. ExThera Medical with the Seraph® has approached for hemofiltration. They used a heparin operated polyethylene (having higher molecular weight) bead-based filter. This technological advancement has helped for isolating a collection of pathogens starting from Staphylococcus aureus (which is resistant to methicillin) to cytomegalovirus without any filtration of drugs which are anti-infectious in nature, and has been confessed an Emergency Use Authorization (EUA) for the treatment of patients affected by COVID-19 [34-35].

3.3. Ex-Vivo Antiviral Approaches

3.3.1. Exploitation of Surfactants. Surfactants are the commonly used as household disinfecting agents possessing higher antiviral activities [36] The exploitation of surfactants to inactivate virus acting as sanitizing agents is shown in [37]. Surfactants are-

- Cationic: present in hair conditioners, antiseptic mouthwash, hand wash.
- Anionic: present in detergents.
- Non-ionic: present as foam also known as emulsifying agents.
Zwitterionic: present in cosmetic products as well as in laundry [38-40]. Though, surfactants using as sanitizing agents are highly beneficial but are rarely used for the construction of virus inactive surfaces. A remarkable research advancement is seen in the use of these antiviral factors for biomaterials applications. The point of view has the potentiality for decreasing the longevity of viruses on surfaces resulting in the minimization of transmission. A quaternary ammonium compound N,N-dodecyl methyl-polyethyleneimine recognized as cationic surfactant with an antibacterial property having envelope of antiviral polymer for its potentiality of rupturing the membranes of cells by interacting with the polycationic chains [41].

3.3.2. Designing of Face Masks. The viral filtration devices most commonly used are face masks. To keep the health of an individual in safe manner, use of masks should become a necessary component to sustain in this present situation. However, designing of all masks are not done only for filtration of virus [42]. Generally, the masks that are being marketed and used are –

- Surgical masks having the capability to filter 3 μm particles by 98% possesses the effectivity to block droplets with large-particle size, but have no ability for filtering aerosolized particles getting mediated by means of sneezes or coughs.
- The capability of performance level face masks like the N95 masks is to filter 95% of 0.1-0.3 μm particles [43-45].

Designing masks having minimal porosity threshold of a virus particle (20nm -300 nm) is very important to reduce spreading of viruses [46,47]. Current research done by focusing on to modify masks with properties of viral deactivation and with multiple uses, higher PPE production and generation of biodegradable wastes. As, most of the masks are produced from petroleum-based polymers having non-biodegradable and non-renewable property causes a huge environmental pollution [48,49]. Thus, to reduce environmental impact in this and future pandemics, it is necessary to tailor masks using biodegradable materials or from materials for multi-use. N95 respiratory masks with copper oxide implementation on it paves the way to mitigate influenza virus. Moreover, incorporating sialic acid, assists mimicking of human cell receptor sites for creating an efficient, easy-to-produce filter which have the capability of eliminating viruses like, influenza [50-52].

3.4. Application of Vaccines

The progress in the manufacture of vaccine for SARS-CoV-2 have themost possibilityto control the spread of COVID-19 encouraging a swirl of research for the fabrication of vaccine as shown in [3, 53]. Previously, the focus for the development of SARS vaccine was given on S protein subunit vaccines and live enervated whole virus vaccines[16,54]. Review has been extensively on the strategies to upgrade the design and fabrication of conventional vaccines by virtue of biomaterials [55,56]. It is known that polymeric materials may act as adjuvants (substances that enhance the antigenicity of an antigen). But the solutions based on multiple biomaterials have also been suggested like, nanoparticles, microneedles, liposomes and scaffolds. For protecting antigen cargo, antigens existing in biomimetic form permitsto target specified immune cells, to fabricate nanoscale structures which can be executed by doing some changes in the material composition, surface chemistry, shape, size of nanoparticle [56,57].

4. Conclusion

In this paper, the opportunities and mitigation strategies of biomaterials for addressing the challenges of COVID-19 are explained. Specific opportunities that are discussed will help not only to fight against the COVID-19 outbreak but also to restore from the adverse socio-economic impacts. This SARS-CoV-2 pandemic has triggered crucial need of urgent testing for diagnosis and boosted up at a larger rate in the biosensing sector. Therapid technological advancement will continue and some part of the work as shown in this review may vary as more research work on COVID-19 becomes available by scrutinizing the results. Various contemporary advancements and future directions in the field of research of biomaterial have been illustrated to combat the challenges of COVID-19.
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