Role of nanoparticles in tackling COVID-19 pandemic: a bio-nanomedical approach

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1. Introduction

Progress in bionanotechnology has inspired the study of interactions between cells and substrates, at both microscale and nanoscale [1], favouring the production of a wide range of nanoproducts for clinical, pharmaceutical, and other applications. Nanoparticles constitute smaller particles that range in size from 1 to 100 nm [2]. According to the International Standard Organization (ISO); nanoparticles cover any nano-objects with external dimensions measuring in nano-scale size between 1 and 100 nm [3]. Naturally occurring nanoparticles include dust, clay, sand, virus, and bacteria [4], while those that are of synthetic origin for example gold, silver, titanium oxide, silica are referred to as the engineered nanoparticles, normally produce from bulk materials optimized for proper interactions in vivo with biomolecules [5], thus show special attributes at atomic, molecular and cellular levels [6]. Due to their unique size and physicochemical properties, nanoparticles are often used for different purposes such as in biomedical sciences, medical, imaging, catalyst, technology-based, energy sciences, environmental, and agricultural [2].

Towards the end of December 2019, a disease with a pneumonia-like syndrome of an unknown aetiology was reported to the World Health Organization office in China [7]. A new strain of Coronavirus was later identified to be the causative agent of the disease and accordingly named as SARS-CoV-2 by the international committee on taxonomy of viruses. Coronavirus belong to the realm \textit{riboviria}; order \textit{Nidovirales}, family \textit{Coronaviridae}, genus \textit{Betacoronavirus}, and subgenus \textit{Sarbecovirus} [8]. These viruses are positive-sense; Single-stranded RNA Virus [9] with nucleocapsid protein [10]. The novel coronaviruses essentially cause severe respiratory illnesses [9,11] that result in several deaths globally. The SARS-CoV-2 strain causes respiratory illness reported in humans [9], other virus strains in pigs and cows, for example, cause diarrhoea [12]. Unlike the two other coronaviruses describe earlier; Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1), the 2019nCoV was established to be often severe respiratory pneumonia-like syndrome [9,13] The disease has spread to many countries mostly via human-to-human transmission. This paper aims to present the role of nanoparticles in tackling the pandemic of COVID-19.

2. Origin, symptoms, and pathogenesis of SARS-CoV-2

Some scholars were among those that thought that SARS-CoV-2 was of zoonotic origin [14,15]. It was reported that 21 out of the 41 early-infected patients to the strain 2019nCoV have direct contact with the local animal market or seafood market in Wuhan China [9], suggesting possible animal-to-human transmission. There has been an earlier report of transmission of MERS-CoV from camel to humans in the Middle
It was now clear that human-to-human transmission [15,16] occurs via coughing and sneezing and even direct contact with an infected person. Viral genome sequencing shows a high similarity between SARS-CoV-2 and bat coronavirus [13,19,20] although there is a need for identifying immediate hosts that serve as a reservoir to this menace. At the initial entry of the virus, an infected person may not present any of the symptoms. Mild to severe Common symptoms including systemic (fever and fatigue), Circulatory (decrease in white Blood cells), Respiratory (shortness of breath, sore throat, runny nose, and sneezing) and Intestinal (diarrhoea) manifest 2–14 days after exposure to the virus [21]. The route of transmission of this novel virus occurs via airways droplet via coughing, sneezing, and direct contact. Replication of this virus essentially occurs in ciliated epithelium cells of the respiratory tract initiating damage of cells followed by inflammation, increase nasal secretion, and rise in mucosa temperature [22]. The virus gains entry into host cells through endocytosis via specific receptors known as human angiotensin-converting enzyme receptor-2 (ACE-2), transcribed, and translate its uncoated genome [22]. New virion emerges from host cells by budding and re-invade new cells.

3. Classifications of nanoparticles

Nanoparticles can be classified as one dimension; size ranges from 1 to 100 nm used in biochemical sensors, optical device, solar cells and systems for storing information; two-dimension nanoparticles; thin layer or single-layered material such as carbon nanotube; and three dimensions; a multi-scale in dimension nanoparticles such as quantum dots, Fullerenes and dendrimers [23]. Nanoparticles can also be categorized into; those generated from the environmental processes such as volcanoes and forest fire; those that are non-engineered are normally generated from power plants and incinerators; those that are engineered for medical and therapeutic purposes. Accordingly, Khan et al [2] have classified nanoparticles into six (Figure 1); (1) metal–base; made from alkali and noble metals; (2) ceramic-based; which are non-metals, inorganic nanoparticles formed via heating and cooling; (3) carbon nanotubes; nanomaterial of the globular, hallow cage as an allotropic form of carbon for example fullerene and carbon nanotubes; (4) semiconductors; possesses properties of both metal and non-metal used in electronic devices, photocatalysis, photo optics; (5) lipid-based; which ranges from 10 to 1000 nm containing lipid moieties; (6) polymer-based nanoparticles; organic-based nanoparticles including nanospheres and nano capsules [2;24].

4. Metal nanoparticles

Metal nanoparticles consist of pure metals; Zinc, Silver, Gold, Copper, Titanium, or their compounds; oxides, Phosphates, Chlorides, Fluorides, and Hydroxides are normally prepared in nano size, 1–100 nm [25]. These particles have been explored as antimicrobial agents with broad activity against viruses [26], fungi [27], and bacterial [27–29]. A study indicated that silver nanoparticles have an antiviral and preventative effect on human influenza virus infection in vitro [30], and in vivo in mouse treated with silver nanoparticles, recording lower level of viral titer and minor pathological lesions in the tissue of lungs that display higher survival benefit during intranasal secondary administration [30].

5. Lipid-based nanoparticles

Lipid-based nanoparticles are made up of lipid vesicles that encapsulate drug or transport lipophilic and hydrophilic drugs to their target. Examples of lipid base nanocarriers include liposomes, bilayers, and micelles. These nanoparticles have received considerable attention owing to their compatibility with the biological system, effective transport within the system, and scaling-up easily [31,32]. They offer many advantages as they have low toxicity, higher stability, efficiency [33], and several other molecules that can be attached to them, thus increasing their specificity. Of the lipid-based nanoparticles, liposome application in advance drug delivery has widely been studied [34] including lipoplexes used in tumour targeting [35] and gene delivery [36]. These nanoparticles are expected to play important role in drug delivery to the lungs for the treatment of respiratory diseases such as COVID-19, Pneumonia, tuberculosis, and asthma.

6. Polymer-based nanoparticles

Polymer-based nanoparticles are made up of colloidal nanoparticles comprising of active therapeutic substances trapped in a polymer [37]. Many advantages of these particles have been studied including drug delivery to the lung [38], inhalation as nanocomposite using salmon calcitonin [39], inhalable chitosan-modified poly composite nanoparticle [40], and drug delivery to pulmonary [41]. Natural polymer-based nanoparticles that are currently used in clinical settings include protein, peptides, and albumin bound paclitaxel used in the treatment of breast cancer [42].

7. Carbon nanotubes

Carbon nanotubes have attracted the attention of many scientists and engineers owing to their specific chemical and physical properties including optical, thermal, electrical, mechanical, and structural diversity. Biomedical applications of carbon-based nanomaterials have also been reported [43]. As carbon allotropes (graphite, diamonds, and amorphous carbon) exist, carbon nanotubes such as fullerene, graphene oxide, and graphene
quantum dots are now becoming popular and highly regarded [44]. Carbon family member has inimitable characteristics and has been widely used in various biological applications including tissue engineering, biosensing, imaging, drug delivery, cancer therapy, and diagnosis [45,46].

8. Ceramic-based nanoparticles

Ceramic nanoparticles consist mainly of metals and metallic oxides, carbides, phosphates, and carbonates such as calcium, titanium, silicon [47] (Figure 1) usually made by heat or heat, and pressure. Many forms of ceramic-based nanoparticles are currently in use, for example, scaffolds, nanotubes, nanoclays with many applications in biomedical sciences such as biosay, drug loading, drug delivery, target cell uptake, and imaging [48] Suitable properties that made these nanoparticles biocompatible include chemical inertness and high heat resistance. Ceramic nanoparticles are regarded as outstanding carriers in the biomedical field for drugs, genes, proteins, imaging agents [47]. To be able to serve as a good and effective drug delivery agent, it is important to monitor different characteristics of nanoparticles, such as porosity, surface properties, size range, and surface area to volume ratio [47].

9. Semiconductors-based nanoparticles

Semiconductors typically show electrical conductivity in between that of conductors and insulators. They are normally formed from group II-VI (CdSe', CdS', ZnSe), III-V (InP and InAs), or IV-VI of the periodic table [49]. The peculiar optical and electronic properties of semiconductors have inspired much work into their possible applications in the design of novel biological probes (cell, protein, and DNA bio labelling) [50] light-emitting diodes' photovoltaic cells' among other tools [51].

10. Applications of nanoparticles in combating COVID-19

Nanoparticles will no doubt play important role in the ongoing fight of COVID-19 by providing several interventions such as nano vaccines, point of care devices, diagnosing devices, nano drugs, drug delivery systems as discussed below.

11. Nano-vaccines development

A vaccine is one of the least expensive and yet effective ways used for the prevention and eradication of infectious diseases [52,53]. Reports indicated that nanoparticles have the advantages of crossing and travelling through biological barriers [54] and act as immuno-stimulant to numerous cell types of the immune system [55]. Poor immunogenicity, instability of vaccines in vivo coupled with toxicity, and the necessity of several administrations are some challenges normally faced with conventional vaccines [56]. To increase the immunogenicity of bioactive peptides, antibodies, and carbohydrates for the induction of powerful T-cell immune responses, modification of targeting moieties surfaces with suitable nanoparticles will be of paramount important [57–59].

The nature of the action of nano vaccines generally depends on hydrophobicity, size, charge, and interaction with biomolecules within biological systems [60]. Nanoparticles can act as adjuvants or carriers of vaccines often referred to, as nano vaccines thus increasing stability, half-life, better stimulation of antibody-mediated and cell-mediated immunity among others (Figure 2). The principle behind this approach involves attaching nanoparticles of size ranging from 1 to 100 nm to an antigen that elicited the immune response and prepared the body to have immunological memory against pathogenic organisms in the future.
Indeed, for the development of nanovaccine capable of conferring immunity against SARS-CoV-2, suitable protein nanoparticles from the viral structural proteins (spike, matrix, nucleocapsid, and envelope) could be delivered to the target immune cells that would elicit an immune response and confers life long immunity to the virus. Spike nanoparticles and adjuvants have been used previously against MERS and SARS-CoV-1 and could also be developed against SARS-CoV-2 [61]. Using hepatitis B viral (HBV) core and bacterial capsids as a model, Storni et al. packaged non-methylated CG motifs into virus-like particles, which induces defensive cytotoxic T-cell responses with no systemic side effect [62]. Pimentel et al. engineered a nanovaccine consisting of a polypeptide nanoparticle with a repetitive SARS-CoV-1 spike protein epitope of approximately 25 nm capable of generating specific neutralizing antibodies to SARS-CoV-1 infection [63]. A synthetic virus-like nanocapsule resembling a viral capsid has been tailored by Matsuura et al. [64], which we thought could also be applied for designing of SARS-CoV-2 capsids for immunization purposes. Nano-sized particles (25 nm) based on antigen specificity and adjuvant systems have been used to promote the delivery of protein/peptide antigen to dendritic cells to stimulate both humoral and cellular immune response in mice [65]. Several nanoparticles, for example Peptide nanoparticle [66,67], cationic polymers [68,69], liposomes [70,71], gold nanoparticles [72,73], nano-bioceramic [74], virus-like nanoparticles [75] and polymer-based particles [76,77] could be employ to boost lymphatic system for generating lymphocytes (B and T lymphocytes) for effective clearing SARS-CoV-2 infection.

Typical challenges for coronaviruses vaccine development is that the comprehensive biological features of SARS-CoV-2 are yet to unravel and the degree of protection caused by inactivated SARS-CoV-1 is insufficient and is unable to prevent SARS-CoV-1 symptoms, while also triggering elevated eosinophilia in vaccinated animals [78,79]. Previous models for coronavirus vaccines are based on spike proteins, recombinant SARS-CoV-1 proteins, DNA plasmids expressed protein or vaccines based on virus-like particles (VLP) [61]. In addition to preventing systemic side effects [61], adsorbing viruses and inflammatory cytokines [80], nanoparticles also enhanced antigen stability, targeted distribution, and long-term release of antigens/adjuvants [81] for optimum immune response.

The activation of CD4 T cells and/or CD8 T cells of type T helper 1 and/or T helper 2 is very important for any designed vaccine (Figure 2). As far as coronaviruses are concerned, T cells have proven promising for immunological memory and protection of infections, for as long as 11 years post SARS-CoV-1 infection in recovered individuals [82,83]. Study shows that DNA vaccine also confers protective immunity and neutralization against SARS-CoV-1 via activation of CD4, CD8, and neutralizing antibodies [84], given this; suitable nanoparticles might be used to deliver DNA vaccines. A screening study has compared epitopes of T cells and B cells in immunological proteins of SARS-CoV-1 and SARS-CoV-2 and concluded that mapping of
the epitopes of T and B cells of SARS-CoV-2 was identical to that of SARS-CoV-1 [85]. Indicating that vaccines developed for SARS-CoV-1 maybe improves for eradicating SARS-CoV-2. Several properties that might be considered for improvement of SARS-CoV-1 vaccines for use against SARS-CoV-2 including preventing systemic symptoms of the virus [61], adsorbing SARS-CoV-2 viruses, and inflammatory cytokines [80], enhancing antigen stability, targeted distribution, and long-term release of antigens/adjuvants [81].

12. Point-of-care diagnostics devices

Points of care device are the devices that are used for carrying out diagnosis at a point where the patient is receiving treatments including hospitals, clinics, diagnostic centres, and medical centres. Point of care devices may be lateral flow devices, paper-based devices, lab-on-chip devices, and lab-on-disc devices (Figure 3). These devices perform fast analysis, reliable, and accurate diagnosis for rapid medical interventions.

Of the advantages of these devices, is during an emergency, for example, the COVID-19, where these devices continue to play role in the rapid diagnosis of cases and isolation of infected patients thereby containing the spread of the virus. These devices offer great advantages due to biocompatibility, fluorescence, electrical and thermal conductivity, magnetism, and specificity to the disease agents and very robust to detect diseases (Figure 3) [86]. One approached to the design of these devices is the use of nanospheres such as gold nanoparticles [87] that has a high affinity to the pathogens, with catalytic properties used in both biochemical and optic devices [34]. Lateral flow biosensors [88] are also been used which operate based on the principle of immuno-affinity chromatography, where antibody specific to the target are added, an antigen normally from bacteria, cell, or protein and secondary antibody tag to the nanoparticle(s) are attached where a sandwich formation is accompanied by colour formation [87]. In this scenario, specific antibodies can be used to detect the SARS-CoV-2 virus rapidly using a biosensor that is accompanied by a change in colour.

Covid-19 testing requires molecular procedures such as PCR, which is cost, time-consuming with lab consumables often unavailable during the pandemic. Nanoparticles offer several advantages such as rapid, affordable, and simple tests that can be conducted remotely without requiring an equipped laboratory. Lee et al. have recently produced nanoplasmonic pillar arrays consisting of gold as a point-of-care test for ultrafast polymerase chain reaction on the chip and rapid detection of infectious COVID-19 [89]. Zhao reported the synthesis of poly (amino ester) with carboxyl groups (PC)-coated magnetic nanoparticles (pcMNPs) and the production of the pcMNPs-based viral RNA extraction method for the sensitive detection of SARS-CoV-2 to resolve issues posed by PCR such as time-consuming [90]. Earlier research used the quantum dot-conjugated RNA aptamer on a chip to detect very low concentrations of SARS-CoV-1 nucleocapsid [91]. Colourimetric assay-based that uses gold nanoparticles have also been documented when capped with adequately engineered thiol-modified antisense oligonucleotides specific for SARS-CoV-2 N-gene detection [92]. A rapid and concurrent detection method for both SARS-CoV-2 and other respiratory viruses using nanopore target sequencing (NTS) has been documented by Wang et al.[93].

13. Nanoparticle-based antiviral therapeutic interventions

Emerging and re-emerging infectious diseases pose threat to global health as the causative organisms adapt to the immediate hosts, moves to new hosts, and develop resistance to the currently available therapies [94]. Currently, there are no approved therapeutics for treatments of COVID-19 patients by the Food and Drug Administration (FDA). Research is still underway to come up with various therapeutic for COVID-19 treatments. The major drawbacks of the existing COVID-19 drugs include lack of specific targeting, resulting in host cell cytotoxicity, which can be solved by the use of organic-based nanoparticles [95]. Among various classes of nanoparticles, metal-based nanoparticles offer several advantages, as they are the potential for targeting viruses with low resistance from viral pathogens [96]. Several studies have indicated the antiviral activities of metal-based nanoparticles including inhibition of influenza virus via binding to the plasma membrane [97], preventing viral binding of hepatitis B virus to host cell [98], interfere with respiratory syncytial virus attachment [99], competitive inhibition of herpes simplex virus [100,101], inactivation of tacaribe virus [102], blocking of viral-host interaction in monkeypox virus [103], blocking of viral attachment to glycoprotein 120 receptor to HIV-1 virus[104–107]. An interesting property of antiviral nanoparticles is non-toxic with a broad inhibition mechanism [108]. Nanoparticles operate via several mechanisms from inhibition of attachment, entry restriction to blocking of viral replication. For COVID-19 and most other viruses, the targeting point of the viral entry point is of a paramount therapeutic intervention [96].

Accordingly, new therapeutics may be designed that target viral attachment of its spike glycoprotein to the human ACE-2, thus prevent viral endocytosis and subsequent release of its genetic material (Figure 4). Nanoparticles can also be made to compete with viral RNA polymerase protein thereby inhibiting the replication of viral RNA. The assembling of different structural viral proteins is an interesting area that may also be targeted to prevent assembling of nucleocapsid, matrix,
Figure 3. Point of care devices and common biological molecules attached for diagnosis. Samples are introduced to the point of care devices in which the sample interacts with various biological molecules attached to the devices produces signal or colour change.

Figure 4. Replication in SARS-CoV-2 and possible therapeutic point of intervention. The virus attached to ACE-2 and enter cell through endocytosis an important point that may be blocked. Upon entry, it released its genetic material, which undergo replication, another step that may be therapeutic intervention point. Nanoparticles may also be used to prevent assembling of viral particles via blocking step 6–7 above.

and spike and envelop to viral RNA thereby inhibiting the formation of the new virion (Figure 4). The versatility of nanoparticles makes them adaptable vectors for the targeting of viruses and the specific delivery of drugs [95].

14. Nano-drugs

Nano drugs are drugs within the range size of nanoparticles of 1–100 nm used to improve drug delivery or organ-specific targeted drug delivery. Several nanodrug
systems were currently in use including liposomes, dendrimers, polymeric nanoparticles, nanocrystals, emulsions, solid lipid nanoparticles, and micelles [109]. Nano drugs will play an important part in ensuring that drug reaches the target tissue for example into the lung where airways are usually blocked in COVID-19 patients.

15. Conclusion

The global spread of COVID-19 across many borders has necessitated the need to explored nanotechnological options available to provide solutions to the current pandemic. Nanotechnological interventions use nanoparticles with size ranging from 1 to 100 nm that mimic viral pathogen or rather attached nanoparticles to antibodies to create nanovaccine and elicit an immune response to confer protection against viral pathogens. The most common forms of point of care devices include lateral flow devices, paper-based devices, lab-on-chip devices, and lab-on-disc devices which operate base on the principle of antigen-antibody reactions, enzyme-substrate reactions, hormonal presence, redox reactions or simply colour formation to detect the presence of substances in patient samples. Many nanoparticles hold promise for antiviral activity through acting as inhibitors of viral entry, competing for receptor binding sites with viruses, inactivating viruses, interfere with viral binding, and blocking of viral replication. Nanoparticles may well play role in targeted and non-targeted drug delivery in patients suffering from COVID-19.

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