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Review

A smarter, tactical approach for combating Covid-19

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ABSTRACT

As human beings, we communicate with each other just like other creatures. In the same way we need to communicate, COVID-19 has to communicate with other viruses. Following the latest Pandemic, combating COVID-19 has become a major need today. Several theories are being formulated and tested for the efficient prevention and treatment of the virus. Vaccination is the ultimate solution but access to the vaccine and getting vaccinated is limited. The purpose of this review paper is to present a new approach. This approach is based on the Quorum sensing of viruses like bacteria. Bacteria use this for communication and it has recently been proven for viruses too. It can be used as a new way or strategy to stop viral communication, therefore restricting the viral spread will possibly help people around the world or reduce the disease's side effects. This new tactic involves the use of functionalized Quantum dots nanoparticles, and when they are coupled with carbon atoms and put to use in different delivery forms, these will be useful for maximum efficacy. The use of carbon quantum dots can be useful to minimize certain possible toxic effects. This may be greatly enhanced by doping boron atoms to the structure to trigger their synergistic effects. We suggest here that the inhaler form of this proposed drug delivery system should simultaneously provide a fairly high efficiency and a less toxic solution.

Keywords: Quorum sensing, Viral communication, Quantum dots, Carbon quantum dots, Pulmonary drug delivery

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INTRODUCTION

Human beings appeared in the world more than 130.000 years ago and so society began . Building social networks needs many interactions between humans and the other social groups. Since their first appearance, they have started to share their experiences and warned others about danger by talking and using other kinds of communication skills. Even today, people like to get as much information as possible from others. Today, the internet and related networks play an important role. According to the Smithsonian National Museum of Natural History reports, a three-year old female baby named *Australopithecus afarensis,* may have been socially active 3.3 million years ago and she might have been able to interact with others. Another two-year-old Neanderthal baby, who was found lying on her back in a deep burial pit inside a cave with a slab of limestone on top of her head, may be telling the unknown story about her death 70,000-50,000 years ago. Scientists found this skeleton in that position and understood that its burial was prepared by others. As we interact with others to enhance our experiences aiming to live longer and better, other creatures also do the same. The theology of "Quorum sensing" (QS) explains how bacteria learn from others (Jiang, Chen, Yang, Yin & Yao, 2019). Bacterial quorum sensing can be activated by the self-produced extracellular signals in the milieu. These signals are mainly produced by certain chemicals which may play key roles in the regulation of bacterial pathogenesis. Some study results showed that these signals participate in the synthesis of virulence factors in microorganisms during bacterial growth and infection (Pearson, Pesci, & Iglewski, 1997; Dietrich, Price-Whelan, Petersen, Whiteley, & Newman, 2006). The synthesis and secretion of these signal-creating chemicals are regulated by these microorganisms (Yarwood, Bartels, Volper & Greenberg, 2004; Carnes et al., 2010). These virulence factors regulated by QS help bacteria to obtain nutrition from the host and evade its immune system. Some scientists believe that if these signal producing chemicals are blocked, this may be an alternative to antibiotics due to its capacity to reduce bacterial virulence and promote clearance of pathogens (Yarwood, Bartels, Volper & Greenberg, 2004; Jiang, Chen, Yang, Yin & Yao, 2019). Some recent evidence (Carnes et al., 2010; Jiang, Chen, Yang, Yin & Yao, 2019) indicates that antibiotic treatments tend to be less effective for patients because of drug-resistance from overuse (Li & Knetsch, 2018; Xu, Dong, Han, Li & Liu, 2018). These days we are faced with a major viral infection, namely COVID-19. The question here is "Can viruses communicate like bacteria?". Some scientists believe that viruses are rather less developed organisms, and they may not have an ability to communicate but, one very interesting and short review published in *Nature* last year explains the secret social lives of viruses (Dolgin, 2019). In this review, Dolgin discussed the possibility of viral communication with evidence to prove it. According to this report, viruses can actually interact with other viruses and are able to make their own decisions. Viruses can control their own destiny according to Wei Cheng, who was described in the report as a microbiologist from Sichuan University in Chengdu, China. Other reports also indicate that the communication skills of viruses work much like the system used in bacteria quorum sensing to share information about cell density and they adjust the population accordingly. It was the first demonstration of molecular messaging between viruses (Erez et al., 2017). This contradictory finding explains that viruses are much more sophisticated and social - they may also communicate using their own kind of language. In fact, this was not clear or useful for anyone until 1999 and maybe after the last COVID-19 pandemic. It was shown that viruses talk and behave like a *Prisoner's Dilemma* strategy game, working in partnership under certain circumstances and acting in their own self-interests in others (Turner & Chao, 1999). It is certain that, to learn this communication pattern and language will help us to learn more about viruses and this will give us more opportunities to combat them appropriately. This may also be useful for eliminating resistances. The shape of COVID-19 is approximately circular with spikes on it. The overall diameter is about 0.3 microns or slightly less, but the spherical core is about 100 nm (Kirtley, 2020). That is roughly 1/100th the diameter of the average human hair. The space between spikes can be reckoned as around 1-20 nm. This can lead us to think that the size of the particles should be in the size range of 1-20 nm if the virus is actually targeted. The particle in this range can be quantum dots (QDs). However, many known QDs are small enough (1-10 nm) but they are highly toxic. They are useful for developing new generation diagnostic kits and may be used for diagnosis only rather than as a carrier for antiviral drugs (Ghaderi, Ramesh & Seifalian, 2011). However, the introduction of new generation non-toxic composite QDs and their potential to be used as drug delivery systems are becoming possible because they are easy to produce with a very cheap technique (Lim, Shen, & Gao, 2014). In addition, some of them can have some other doping atoms such as nitrogen or boron. Known and previously developed QDs have been produced from CdSe, InAs, CdS, GaN, InGeAS, CdTe, PbS, PbSe, ZnS, and ZnO so far. The reason they are called QDs is because the band gap can be changed by changing its dimensions. In other words, size is a controllable parameter in QDs, and when this feature is combined with the effect of 'quantum confinement', QDs can gain some extraordinary optical and electrical properties (Degim & Kadioglu, 2013). With the change of the dimensions of the QDs, the color of the emitted light changes with the effect of quantum restriction (Figure).

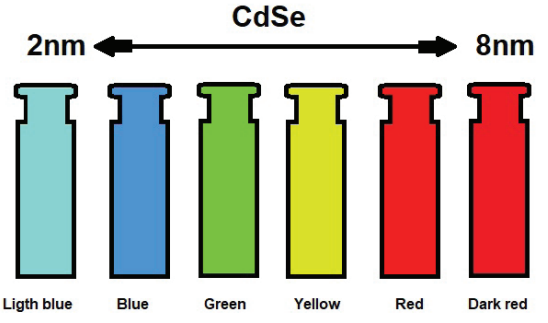

Figure 1. The color of Quantum Dots depending on their sizes.

While the smallest size QDs look blue, large QDs emit red light (Girma, Fahmi, Permadi, Abate, & Chang, 2017). QDs generally have very toxic effects since they are made up of metal atoms. Even though the quantum point, which has very superior properties, is generally made, their toxicity could not be

reduced causing a major problem. The ultimate effect and the real biodistributions or changes of biodistributions of QDs in the body have not been fully understood or determined yet. At this stage carbon quantum dots (CQDs) appear to be the safest nanoparticles to be used for medical purposes. In recent years, the production and preparation methods of CQDs have been proposed. The very futuristic usage of CQDs has been shown in the literature. The use of carbon materials including CQDs is generally accepted as safe. Carbon materials are also known to be adsorptive materials, being quite useful to deliver the drug molecule by simple adsorption and subsequent desorption. If the carbon material is good enough to carry, the drug molecule can be released at the site of action by desorption. It is a rather easy procedure, and the material is known to be safe. The only problem is the size of the carbon material because while in many cases the material is safe when it is in a bigger form, it can be very toxic if it is in a nanometer size. Moreover, in many other particulate products, nanoparticles (NPs) have been widely used in diverse food fields, including food processing, safety assessment, packaging, and nutrition delivery (Duncan, 2011; Bi et al., 2017). These NPs may potentially enter the body *via* several different routes such as inhalation, ingestion, or uptake through the skin (Martin et al., 2011). All these show that some nanoparticles may be safe for use. It is very interesting that when NPs are exposed to biological fluids or when they enter the body, they will probably be covered immediately with the protein or be covered to form a kind of protein corona on the nanoparticles (Yan et al., 2013; Huang, Carney, Ikuma, Stellacci & Lau, 2014). This indicates the affinity of nanoparticles to protein. If NPs are smaller, this version of nanoparticles can be QDs. The attraction of protein to the QDs may be increased. The interaction between nanoparticle and protein also affects the toxicity (Chen, Ganesh, Wang & Amiji, 2017; Chen, Ganesh, Wang & Amiji, 2019). The formation of the protein nanoparticle complex depends on size, chemical composition, and surface characteristics (Nayak et al., 2019). W. Hu et al. reported that carbon material (graphene oxide) can form a complex with 10% fetal bovine serum, thus mitigating the cytotoxicity (Hu et al., 2011). Coating graphene oxide with bovine serum albumin significantly attenuated its toxicity.

Food-borne CQDs have been found in roast salmon after the flesh of the fish was heated at about 200°C for 50 minutes (Song et al., 2019). When the roast salmon is consumed, the CQDs are inevitably transferred into the circulatory system. It is possible to get CQDs when we eat roasted salmon. These CQDs may not be very dangerous. These food-borne CQDs might encounter various kinds of serum proteins and be absorbed by these proteins via interactions of the functional groups (Zhu, Wang, Sun, Liu & Wang, 2010). Among the serum proteins, human serum albumin (HSA) is the major soluble protein constituent (40 mg/mL) in human blood plasma with many physiological functions (Arumugam & Malaichamy, 2015) and it has been shown that CQDs can interact with proteins in the body (Song et al., 2020). The formation of the human serum albumin (HSA) and CQDs complex, like a corona from roast salmon, as well as its biological effects, including acute toxicity in mice, have been investigated. The HSA-CQD complex has been introduced because of its static binding mechanism (Yi et al., 2004). The HSA-CQD complex mentioned enters the cytoplasm and has been found to be present in lysosomes or autolysosomes. The HSA coronas have been reported to mitigate the cytotoxicity of CQDs from 18.65% to 9.26%, and the energy metabolism was rectified from glycolytic to aerobic metabolism (Song et al., 2020). This shows the detoxification mechanism and the affinity of proteins to the CQDs. The COVID virus has proteins (S1 and S2) to bind to the receptor to enter the cell. It has been reported that if the S protein is blocked with a molecule, it can be used for preventing the host cells from COVID entering (Yi et al., 2004). If CQDs are not very toxic and we consume them without noticing without having toxicity problems, they may be useful for preventing COVID infections. Because CQDs are capable of interacting with proteins and the corona virus has a protein to enter cells, we may be able to stop the virus using CQDs. A very interesting study result showed that QDs made from tea leaves destroyed lung cancer cells (Shivaji et al., 2018). Their research confirmed previous evidence that tea leaf extract can be a non-toxic alternative to making QDs using chemicals. The cadmium sulfur (CdS) QDs derived from tea leaf extract is reported to show exceptional fluorescence emission in cancer cell bioimaging compared to conventional CdS nanoparticles but Cd is still not very good to use being a quite toxic or even carcinogenic element. However, all these show us that QDs can be a good alternative for the therapy of lung diseases including COVID-19.

Alongside this, another very interesting paper appeared in the literature highlighting the positive effect of functional CQDs as medical countermeasures to human coronavirus (Loczechin et al., 2019). Researchers produced a series of functionalized CQDs. They tested their functionalized CQDs in terms of antiviral activity. It was very interesting to note that all boron functionalized CQDs were found to be antiviral. Moreover, they found that the antiviral effect was maximum (EC50=5.7 mcg/mL) when they functionalized their CQDs with amino boronic acid. Authors claim that the underlying mechanism of the action of these CQDs can due to the inhibition of the virus entry receptors by the interaction of functional groups of the CQDs; the activity was reported to be observed at the viral replication step (Loczechin et al., 2019). If the boron containing CDQs are effective for the therapy of COVID-19, boron compounds or boron doped CQDs may be a better alternative.

Strategy

The strategy should be logical when viruses are subjected to drug treatment. The delivery system should be in a proper size range to interact with the virus body and be able to pass through the spikes and should reach to the virus' spherical body. More than that, the drug delivering nanoparticle should destroy the communication ability of the virus or destroy the viral message. This can be a smarter way to combat COVID-19 - one of the century's biggest problems. The strategy should target the virus directly. To administer a drug and wait for it to reach enough concentration in the lungs or other target tissues requires more time and higher doses because of the elimination, metabolism and hepatic first pass effect. Therefore, the drug should be administered directly in a proper formulation.

Administration rationale

COVID-19's target is lung epithelial cells therefore our target for stopping viral entry should be the epithelial surface of the lung. If this is the case, we can deliver the drug formulation using an inhaler; drug formulation can be sprayed and delivered by inhalation. To be delivered by inhalation, the drug formulation should be in solution or dry powder form. A solution form can be more useful because if a powder form of CCQDs is going to be used, the actual particle size will be quite small. Particles can reach the deeper sites of the lungs and alveoli but they can be exhaled as well. If the spray form is applied to the lung by inhalation the droplet size can be controlled better using a proper spray head and proper pressure. Also, it can be sent to the site of action much better. When CCQDs reach the surface of the epithelial cells in alveoli they can interact with COVID-19 viruses and block the adhesion or viral replication.

CQDs are a new class of fluorescent carbon nanomaterials having an approximate size in the range of 2–10 nm, as mentioned earlier. The majority of the reported review articles have discussed the development of the CQDs, especially their use in bio-imaging and chemical-/biological-sensing. However, there is still a severe lack of consolidated knowledge on the recently developed CQDs (especially doped/co-doped) and their therapeutic effects. Still, there are number of works in the literature indicating a number of recent developments in doped and co-doped CQDs using boron (B), fluorine (F), nitrogen (N), sulphur (S), and phosphorous (P) (Kandasamy, 2019). The green synthesis methods of this boron doped CQDs has also been introduced (Bourlinos et al., 2015) but the many extraordinary properties of these CQDs still need to be discovered.

CONCLUSION

Looking at all these theoretical and aspects, and compiling the results, it appears that CQDs can be considered as a better delivery system for effective and rational therapy for life-threatening diseases including COVID-19 infections. Other atom doped CQDs in particular appeared to be the most effective. To deliver the drug to the lungs in a spray form may be another alternative because the final target is the epithelial surface of the lungs. This system can simply be transferred by inhalation of the sprayed solution of CQDs. It may be a better strategy to stop the virus at the entry site. These can be a starting point for the development of as effective solution. We strongly believe that these results and points of view will help readers to think through new pathways which will open a new window for new and better strategies to fight diseases.

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