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Current therapeutic protocols for COVID-19 and promising nanotechnology solution

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Abstract

The global health crisis of novel coronavirus disease (COVID-19), that is caused by SARS-CoV-2 a new virus recently discovered in Hunan Seafood market located in Wuhan, Hubei Province; China in December 2019, that resulted in severe acute respiratory infections, with critical complications among old and who are immunosuppressed people. There are common drugs usually available for reducing complications, however; resistance to those drugs has been developed by (SARS-CoV-2) virus, which leads to a

remarkable loss of efficiency of these medicines. in this regard, applications of nanotechnology appear to extremely exhibit excellent options to solve this problem. This review investigates the currently available drugs and alternative drugs used for the potential therapy of (COVID-19) symptoms with focusing on nanotechnology to address this pandemic.

Keywords: COVID-19; SARS-COV2; Underdeveloped medicine.

Introduction

A broad family of viruses known as Coronavirdea from which a novel virus called SARS-CoV-2, has evolved. It is thought to have an origin of zoonosis and has a great genetic resemblance to bat coronaviruses [1, 2]. It is a newly discovered, emerging infectious disease after an outbreak in Wuhan, China, in December 2019 and has been known as the main cause of respiratory infection outbreak among people [3-5]. The name of COVID-19 disease (formerly known as the "2019 new coronavirus") caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Coronavirus has been officially announced by the World Health Organization (WHO) [6, 7]. Animal coronaviruses are infectious to people but, in rare cases, and then it can spread among people possibly, such as with Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV), and now with this new virus (named SARS-CoV-2) [8-11]. Based on the statistics of the World Health Organization, more than 5103006 confirmed, 2110000 recovered and 333401 deaths have been recorded around the world and about 4272 confirmed cases of COVID-19 in Iraq; 152 deaths; and 2585 patients who have recovered [12]. A developed test which is the Real-time reverse transcription-

polymerase chain reaction (rRT-PCR) has been performed to qualitatively diagnosis COVID-19 infection [13, 14]. The samples can be obtained from nasopharyngeal swabs or sputum for this test [15, 16]. The test requires only a few hours to 2 days to show the results. A new test has been approved by the FDA by Abbott Labs which utilizes the technology of isothermal nucleic acid amplification instead of PCR [17]. This method can provide positive results in less than five minutes and negative results in only 13 minutes. Computed tomography CT for chest of infected patient contributes with positive RT-PCR test for quantitative determinants [18-20]. Most of the infected people were elderly and immunocompromised [21, 22]. So far, there is no effective vaccine or specified treatments for COVID-19. However, there are several clinical trials underway to evaluate potential treatments [23-25]. it is highly recommended to use vaccination to preventing disease and its complications that occur mainly in high-risk groups like children, elderly patients, patients with chronic respiratory diseases and pregnant women. patients treated with antivirals without delay can reduce the threat of severe complications; however, this virus still poses a real problem in drug resistance [27, 28].

Nanotechnology is a promising technology that can be broadly used in the medical field, especially for diagnosis and treatment of cancer, stroke, neurological disorders, bacterial, and viral infections [29]

There is ongoing research in addition to efforts by nanoscientists over the world to provide updated information that helps or enables scientists to Improved detection of SARS-CoV-2 virus, reduce infection levels by producing nano-facemasks, and intelligent nano-drug delivery systems for targeting viral infections [30]. Thomas Webster has developed nanoparticles with very small sizes (hundreds of times smaller than SARS-2), that can

adhesive to the virus and destroy it by using an external infrared light field [31, 32]. Nano- compounds could be designed to loading anti-inflammatory agents such as adenosine, which could be used to decrease abnormal immunological reactions eg cytokine storm [33, 34]. On the other hand, Nanosensors are also exhibiting the active capacity to detect viruses at minimum concentrations to predict infection before symptoms have occurred [35, 36].

Nanoparticles can stick to the surface of the viruses such as Ebola or influenza and then destroy these viruses by chemotherapy after using infrared wavelengths [37].

Nanoformulations show a promising solution for the treatment of viral infections via delivery of antiviral agents to the targeted tissues such as liposomes, nanoemulsions , magnetic nanoparticles, and nanosuspensions were investigated for drug delivery of antiviral drugs for both in vitro and in vivo studies with possible to be applied in clinical practice figure 1 [38, 39].

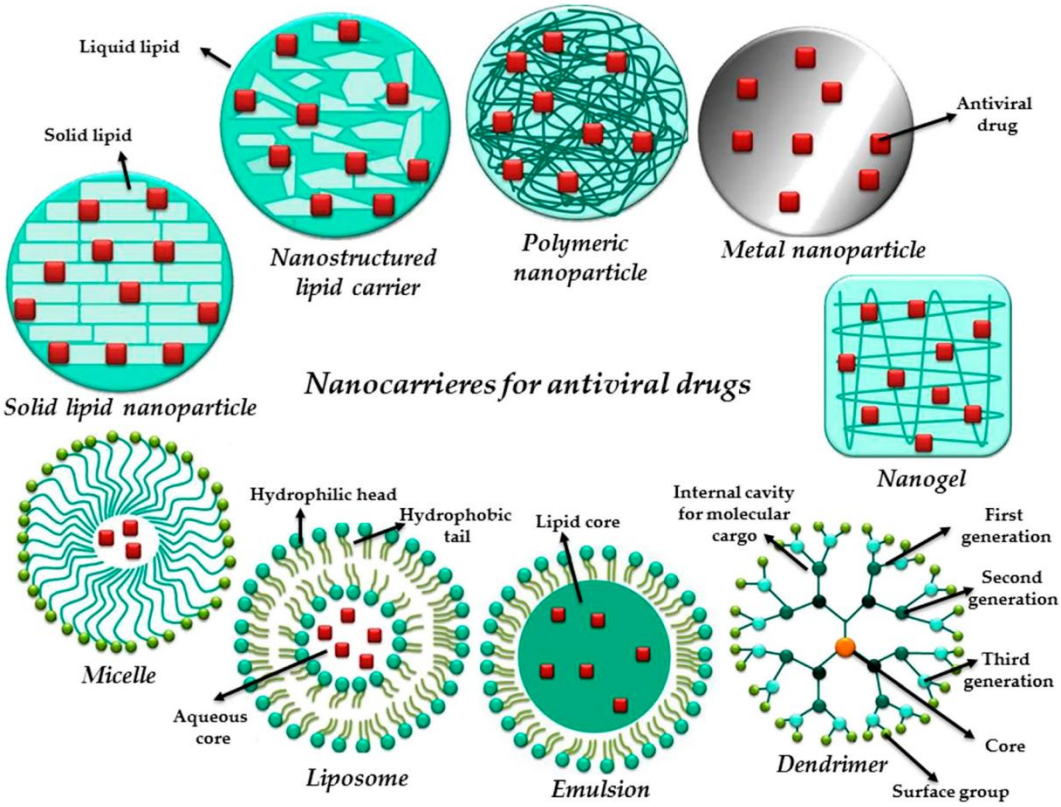

Figure 1. Nanostructured lipid carrier, Polymeric nanoparticles , metal nanoparticles, nanogel, denderimer, emulsion, liposom, micelle and solid lipid nanoparticles [40-45]**.**

This review article summarizes drugs currently used to hope will help fight COVID-19 and a promising nanotechnology solutions.

Live Cycle of COVID-19

SARS-CoV-2 entry is the first step of viral infection then the virus begins to penetrate the host cell by the binding of spike protein (S) to the ACE2 receptor on the cell membrane [29]. Then, S protein is changed to make it easy to the viral fusion through the endosomal membrane [30]. Then, the virus targets their genome to the host nucleus, RNA is released and translated into viral

enzyme replicase and this is result in two types of proteins, polyproteins pp1a and 1ab, and from these two proteins the different subunits of the viral replicase/transcriptase in addition to accessory proteins of as yet unknown function are derived by proteolytic cleavage, [31]. The viral polymerase results in a complex of subgenomic mRNAs by discontinuous transcription and last are translated into relevant viral proteins. Genome RNA and viral proteins are later amalgamated of the endoplasmic reticulum (ER) and Golgi network and subsequently vesicular transported and released out of the cell [32] Figure 1.

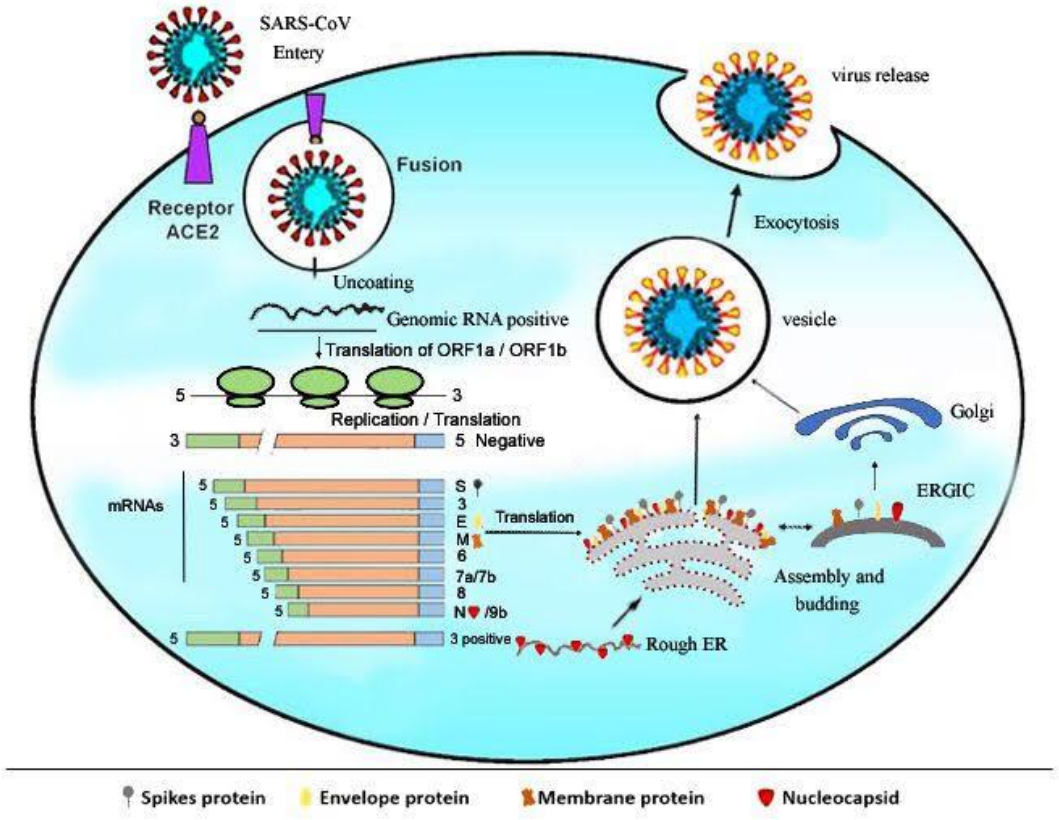

Figure 1. Life cycle of SARAS-COV. The binding of S protein with host cell factor (ACE2)129 and entrance of virus particle into the target cell, the ACE2–virus complex is then translocated to endosomes, where S protein is split into small products by viral proteinases to stimulate its fusion activity**.** Subgenomic

negative-strand templates serve as templates for mRNA synthesis. genomic RNA and N protein in the cytoplasm play a role in the assembling viral nucleocapsids. The virus then then released from the cell through exocytosis.

Treatment

Unluckily, there is no treatment approved by FDA for COVID-19. However, researchers are continuously making a great effort to find effective treatments or vaccines for this serious infection [33, 34].

New drugs have been approved for special health conditions, as possible for COVID-19 treatment [24, 35]. China's experience for containing and treating COVID-19 infection, has proven to be effective, and have followed by medical practitioners in many countries [36-38], clinical practice guidelines in China was set up in January 2020, for treated patients in the hospitals associated with COVID-19 infection by using α-interferon [39, 40] incorporated with the repurposed Kaletra drug [7, 27, 46], (which is a mixture of ritonavir and lopinavir (an approved mixture of the HIV protease inhibitors) [47] and this medicine combination could supply some clinical advantages as reported by WHO [48], Kaletra had also been studied in the treatment of both SARS and MERS coronaviruses [49]. and also studied as a possible COVID-19 treatment [50]. Kaletra was tested together with other reused drugs whose mechanism of action is targeting fragments of the replicated machine of other viruses having the same behavioural patterns like COVID-19, e.g. ribavirin which has the characteristic of guanosine analog and RNA synthesis inhibition, also emtricitabine/ tenofovir Alafenamide fumarate which has the ability to inhibit reverse transcriptase or Umifenovir which is a dual-acting direct antiviral drug used for prophylaxis treatment of viral influenza and used in Russia and china [7, 51].

SARS-CoV-2 is enveloped, with a RNA which is a positive stranded and has a somehow big genome around 30 kb and containing four structural proteins, named, spike (S), nucleocapsid (N) envelope (E), and membrane (M) [52].
Kaletra is a drug known as a ritonavir-boosted lopinavir composite which is frequently used for the treatment of human HIV and also shows inhibition activity against 3-chymotrypsin- protease enzyme in coronaviruses such as SARS and MERS [53, 54].

There are many scientists and researchers targeting the design of efficient drugs toward COVID19, especially focusing on antiviral drugs [55]. Such drugs include penciclovir, whose target is DNA polymerase of herpes virus, and lopinavir/ritonavir, which attack the protease of HIV [55], with the importance of indicating that coronaviruses do not contain or use a reverse copy of copies [56]. So that it's preferable to focus on the RNA-dependent RNA polymerase and similar versatile enzymes of RNA viruses [51].
There are multiple clinical trials by using singular Kaletra drug or combined with different mixtures of interferons, inhibitors of guanosine-analog RNA-synthesis, or combination with antiviral medicines like Baloxavir, Oseltamivir, Marboxil, and umifenovir [57] (Table 1).
Remdesivir is considered a novel antiviral drug in the class of nucleotide analogs [57]. The reason why there was a repurposing of Remdesivir is that its activities against viruses may make it effective as an anti-SARS-CoV-2 treatment [58, 59]. besides, is some clinical trials has utilized Remdesivir drug and indicated that has high activity among different coronaviruses, and it could be used as the major candidate for testing [59]. The recent reports of WHO regarded Remdesivir one of the main promising drug for COVID-19 treatment

according to its high broading activity for both in vitro and in Vivo against coronaviruses and safe utilization in case of Ebola viral disease trials [60, 61].

There were some researches recently published in January under in vitro model and have revealed the broad activity of Remdesivir against an isolate of SARS-CoV-2 clinically [59, 62] Further, experimental studies on mice related to MERS have proven that this drug has improved lung function better than the lopinavir/ritonavir mixture.

Another approved antiviral drug used for remediation of influenza A and B called Favipiravir, which has broad-spectrum activity and acts as an inhibitor of RNA polymerase enzyme3 [63]. However, in vitro experimental studies did not show the high activity of this drug in clinical isolates of SARS-CoV-2.

Prezcobix is another antiviral drug and acts as HIV protease inhibitor, and experimented for evaluation of its activity against COVID-19 [64].

Hydroxychloroquine and chloroquine drugs are approved by FDA as antimalarial and autoimmune disorders and recently these medications were investigated after numbers of experimentally clinical trials before and after exposure prophylaxis of COVID-19 infection and treated the patients with severe, mild and moderate symptoms of COVID-19 [65].

Use of the chloroquine and hydroxychloroquine treatment has been authorized by FDA issued an Emergency Use Authorization (EUA) as a clinical treatment of hospitalized adults and adolescents (weight ≥50 kg) suffering from COVID19, but with restrictions placed on the use of these medications [66].

The majority of the above-reported drugs in clinical trials act as inhibitors for elements of the coronavirus life cycle [67]. Umifenovir, chloroquine or interferon block the entrance of the virus into the host cell, whereas some medicines work through inhibit 3CLpro and then prevent viral replication such as lopinavir/ritonavir, ASC09 or darunavir/cobicistat, while act Remdesivir,

favipiravir, emtricitabine/tenofovir Alafenamide or ribavirin via inhibiting the synthesis of viral RNA [68].

The strategy for entering the SARA-COV2 into the cell involves the binding of the virus's spike glycoprotein to the host cell receptors using Angiotensin-converting enzyme 2 (ACE2) and the cellular protease transmembrane protease serine 2 (TMPRSS2) [69]. According to an unpublished preprint [70] the marketed TMPRSS2 inhibitor camostat mesylate blocked the cellular entry of the SARS-CoV-2 virus.

Table 1. Common drugs in treat COVID-19.

Drug	Action	Ref.
Chloroquine or hydroxychloroquine	Endosomal acidification fusion inhibitor	[65]
Baloxavir marboxil ,favipiravir and the combination of lopinavir and ritonavir	Baloxavir marboxil act as an inhibitor of cap-endonuclease enzyme	[57]
	favipiravir prevents viral genome replication by selective inhibition RNA polymerase, (for influenza A and B)	
	the combined therapy of lopinavir and ritonavir are acting as protease inhibitors for (HIV) treatment	
Oseltamivir, ASC09 and ritonavir drugs	ASC09/ ritonavir drugs inhibit the HIV-1 protease, Oseltamivir is act as an inhibitor for influenza virus sialidase	[69]
Azvudine	act as an inhibitor for the enzyme	[66]

	(nucleoside reverse transcriptase) against HIV-1/AIDS	
HIV drugs: lopinavir , ritonavir , with or without umifenovir	Sequentially, these group of drugs influences by inhibition HIV-1, HIV/AIDS protease, and influenza (experimentally)	[68]
Remdesivir	The prodrug of an adenine analog "Phosphoramidate" which is utilized for Ebola and Marburg virus outbreaks and has the same action of HIV reverse transcriptase inhibitors	[71]
different combinations of darunavir/cobicistat alone or with lopinavir/ritonavir and thymosin α1	Darunavir and cobicistat drugs are respectively, used as inhibitors for HIV-1 protease and cytochrome P450 (CYP)3A enzymes, and approved as a combined therapy against HIV-1/AIDS. Thymosin α1 a strong agent for modulating immune response and inflammation.	[69]
Interferon alfa-2b alone or in combination with lopinavir/ritonavir and ribavirin	Interferon alfa-2b is a recombinant cytokine with antiviral properties; ribavirin is a guanine derivative; as above	[72]
Methylprednisolone	Synthetic corticosteroids that have a binding activity to nuclear receptors to inhibit proinflammatory cytokines	[73]
Camrelizumab and thymosin	Camrelizumab act as an inhibitor against PD-1 checkpoint it is a monoclonal antibody humanized and act with thymosin to prevent sepsis in patients infected with	

Tocilizumab	COVID-19 Humanized interleukin-6	mAb	targeting	[74]

Zinc, Vitamin D & C

Together with the drugs that have been tested to control COVID-19, there are home remedies that may protect or reduce symptoms of respiratory infections and decrease the risk of the disease [75]. Sufficient amounts of Zinc have been noted to speed up recovery from some viral infections when taken right away [76]. Studies have indicated the same results by using different formulas such as zinc lozenges, syrups, and tablets. The NIH notes that the body needs zinc and zinc is essential to create white blood cells which are potential elements in fighting infections. However, overdoses can do more harm than good, and this is along with all supplements that should be taken with the consent of your doctor [77].

Vitamin D has been studied many times to be used in treating respiratory infections. Based on the evidence that the people suffering from tuberculosis and pneumonia are more likely to be deficient in vitamin D [78]. Due to the antioxidant activity of vitamin C, at least one of the chines hospital put vitamin C into a phase 2 clinical trial during the COVID19 outbreak, hope that it reduces the lung inflammation that may lead to death [79].

Chinese scientists have been studied the possibility of the use of stem cell therapy of infected people with the coronavirus, and there are scientific reports indicate that the patient that receives stem cell therapy while in a serious COVID19 condition has been released from hospital after recovering [35, 80].

Stem cell therapy has also been used in treating H7N9 avian flu and showed good results [81]

Ivermectin

Ivermectin is anti-parasitic drug that has been used for decades as veterinary medicine against parasitic infestations and is also prescribed by doctors to treat head lice, scabies and other infections caused by parasites. It is well approved by the FDA. In recent years, this drug has been demonstrated for treatment against a wide range of viruses for in vitro studies and it was identified as an inhibitor factor for HIV-1 protein integrase, [82]. Caly L et al reported that a single dose of Ivermectin drug stopped the replication of SARS-CoV-2, under in vitro conditions [83, 84]. Therefore, this drug needs active efforts of studies to benefit from it as a promising treatment of COVID-19, in the future.

Nanotechnology can develop nanoscale sensors for quick detection of SARS-CoV-2 instead of the traditional time-consuming diagnostic tests, and these include gold nanoparticles, iron oxide nanoparticles, graphene, quantum dots, carbon quantum dots and carbon nanotubes [85-87]

Fabrication of nano-scale TiO2 filters, Ag NPs and carbon mat nanofibers for active filtration to control airborne viruses [88-90].

Providing active antiviral protection by the synthesis of nanoscale coatings materials such as gloves, masks, and lab coats for doctors , and nurses [91-93].

In summary, the treatment of COVID-19 will still be a challenge. The viral structural component is currently the target of the many promising drugs profit from nanotechnology. In recent years, a great number of drugs have been developed and investigated to modulate host cell response and because of its activity against different viral strains, Nanoscale-based drug delivery vehicles

offer novel options to overcome the limitations associated with traditional antiviral drug therapy and these compounds have much of interest that may constitute promising new agents in COVID-19 infection treatment.

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