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Nanotherapeutics: A Way to Cure Cardiac Complications Associated with COVID-19 †

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Abstract: The outbreak of SARS-CoV-2 has caused a catastrophe in the world. With significant efforts from the medicine and scientific communities, millions of people all around the world have been vaccinated. Irrespective of that, individuals are getting infected due to mutations in the virus. Noticeable aftermath damage is seen in most of the major organs of the body. Although it is primarily a respiratory infection, the previously healthy patients have mostly developed cardiovascular diseases. Natural products can be used as a cure to such newly developed diseases. Targeted drug delivery of natural products through nanotechnology (nanoparticles and nanorobots) can be an efficient way to tackle this modern-day problem. This review aims to discuss the ways nanotherapeutics can be used to treat cardiac complications. Essentially, it will help to develop an idea that can be used in the future as a solution to the problem under discussion.

Keywords: Cardiovascular System; COVID-19; Herbal medicine; Natural Products; Nanotechnology; Nanorobots; SARS-Cov-2.

1. Introduction

The outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was identified as a pandemic within the year 2020 by the World Health Organisation (WHO) [1]. The infected patients often presented with symptoms like fever, fatigue, cough, shortness of breath (or dyspnea), and other symptoms identifying respiratory distress [2]. Following the mode of transmission and the presented symptoms, the disease was identified as a respiratory infection. With the absence of any standardized treatment protocol, a call for urgency in research was felt. Slowly the symptoms of the disease were studied and the effect of the virus on the various parts of the body was analysed. By 2022, this viral disease has been identified as a multi-organ disease [3].

This review will discuss briefly the various manifestations of the viral disease with a primary focus on cardiovascular complications. Discussions will be carried out on the natural products that have the potential to cure cardiovascular alignments. Following which discussions on the role of nanotechnology in the pandemic and its potential to cure cardiovascular complications are present. And finally, the review will provide some strategies by which nanotechnology can be used as a treatment option for such complications.

2. Viral Infection and its effect on the human body

2.1. Pathophysiology of SARS-CoV-2

SARS-CoV-2 is a pathogenic betacoronavirus and human beings act as its host. The virus utilizes a plethora of cellular components of the host cell to ensure replication and exponential growth within the host body. It is generally seen that the patients or infected

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individuals show clinical symptoms within 2 to 14 days of exposure to the virus [4]. The pathophysiology has been detailed in Figure 1.

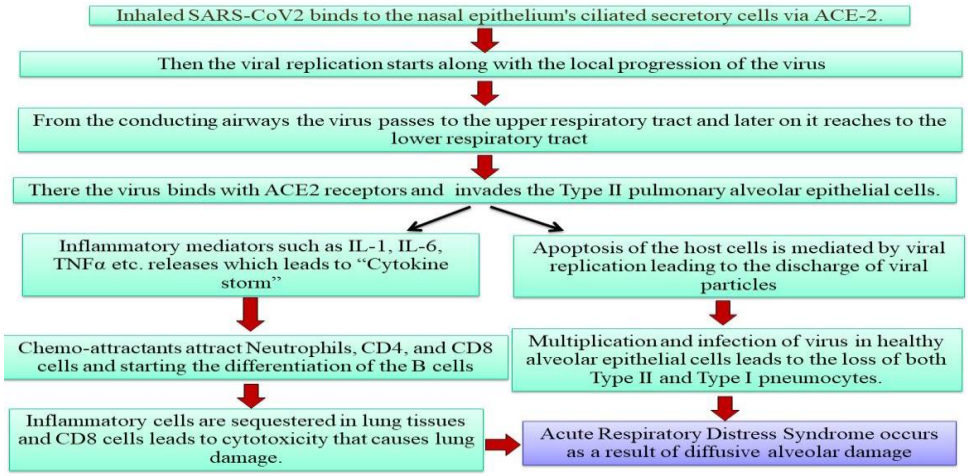

Figure 1. Pathophysiology of COVID-19 adapted from [5].

2.2. Effect on the Major Organs of the Body

After entering the body, the virus causes a major increment in the levels of pro-inflammatory cytokine in plasma. This phenomenon is now termed as "Cytokine storm" [6]. This causes systemic inflammation within the body and can be identified as one of the reasons for the damaging effects on the organs and the disruption of the normal functioning of the same. Lungs show signs of acute alveolar damage and the presence of alveolar fibrin aggregation. Acute kidney injury is seen within patients and has caused an increase in mortality rate. In the brain, there were signs of severe damage which proves that the virus has neurotropic and neuroinvasive properties [7]. The liver shows signs of minimum damage. Biopsy of the liver of COVID-19 positive patients revealed mild lobular and portal inflammations [8, 9]. Complications in the GI tract are very common and in the worst-case scenario require surgical intervention. Endoscopy of a few patients revealed intestinal mucosal damage which clearly shows the ability of the virus to infect the GI tract. A higher level of lipase, amylase, and acute pancreatitis proves pancreatic damages caused by the virus [6, 10].

Other than the major organs, the constituents of human blood also get altered due to COVID-19. As mentioned before, there is a hyperinflammatory response of the body due to the infection. The count of platelets reduces and the fibrin degradation products or D-dimer increase within the blood. This causes the initiation of abnormalities within the normal coagulation process and further might lead to death due to multiple organ failure [6, 11]. In this context, cardiovascular complications are one of the major issues of the clinical manifestations due to COVID-19. This has taken countless lives and therefore, is an important aspect to focus on. This review primarily focuses on cardiac complications and proposes some strategies to deal with the same.

3. Cardiovascular health and related complications associated with COVID-19

Cardiac manifestation has affected not only the individuals with pre-existing cardiovascular issues but also the people with no history of cardiovascular diseases. Among the various complications seen, myocarditis and heart failure are the most common. The attack of the virus on the myocytes has caused damage in the heart but the exact pathophysiology of the same is not clearly known [12]. The concentration of the increase in the sensitivity to cardiac troponin 1 levels can be pointed out as the primary reason for the abnormality seen in the heart [13]. This increment causes ischemic cardiac injury which in the long term translates to coronary artery disease.

Another probable pathway of cardiac damage is caused by the surge in myocardial oxygen demand. As the virus affects the lungs and causes respiratory distress, the oxygen demand is never met which translates to damages [12]. The pathophysiology has been further described in Figure 2. The initial stages of the viral infection sometimes showed malfunction of the respiratory system and in the later stages, the cardiac complications were more pronounced. Other than that, arrhythmias (tachycardia, bradycardia, and asystole) are a common part of cardiovascular complications associated with COVID-19 infections [6].

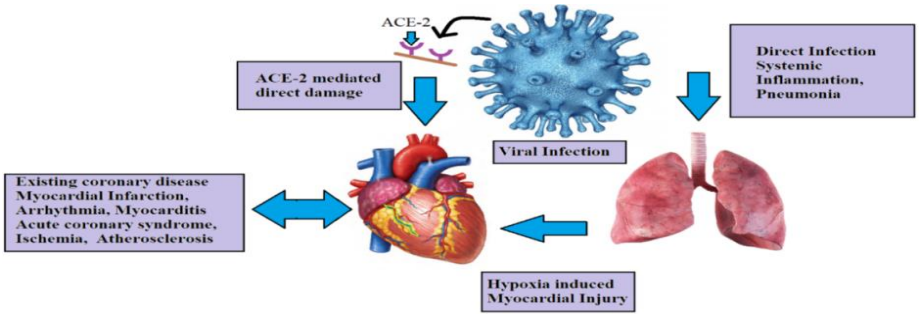

Figure 2. Probable cardiovascular complications associated with COVID-19 adapted from [12].

4. Nanotherapeutics in COVID-19

Nanotechnology has been used extensively in developing vaccines and also as a diagnostic tool in COVID-19. Nanobiosensors can be used as a diagnostic tool that is both extremely sensitive as well as cost-effective. In this case, a biotinylated DNA aptameric silver nanoparticle can recognize the entire inactive virus. There are many such examples of nanobiosensors that effectively do the job of recognising the entire virus or a certain element of the virus (like spike protein or nucleocapsid protein) [14]. Silver, gold, zinc, graphene oxide, and gold nanoparticles also show intrinsic antiviral properties. They can be used as antiviral agents and for the treatment of viral infection [15].

Nanoencapsulation is the product from merging vaccination and nanotechnology. Encapsulation of the viral genome can do the work of vaccination without any significant side effects. Pfizer-BioNTech developed one such vaccine within liposomal nanoparticles or PEGylated liposomes (BNT162b). Inside those nanoparticles and liposomes, the mRNA has been incorporated. Such formulations are stabilized as they are designed in a nano form. Additionally, it has completed the Phase 3 clinical trials with flying colours. Moderna also has prepared similar vesicles to deliver their vaccine made from mRNA [16].

Therapy assisted with nanotechnology is a good option because multiple drugs can be administered at a time. The drugs can be loaded within nanocarriers and they can control the severity of the disease by controlling the systemic inflammation [15].

There is no standardized treatment protocols available to treat the clinical manifestations associated with COVID-19. But based on previously done experiments, probable treatments can be obtained. For instance, pulmonary fibrosis is a very common effect of viral infection. So, in a previous study, it was proven that hydroxychloroquine modified by cholesterol that is encapsulated by liposomes can be used to treat pulmonary fibrosis. Therefore, the same formulation can be used in the case of COVID-19 induced pulmonary fibrosis as well [17].

Nanorobots can be a great help in this situation by increasing the precision in treatment and medicine. During the pandemic, the use of programmable nanorobots allows for the detection of varied quantities of certain proteins in the bloodstream which could aid in the identification of a specific virus. The development of proof-of-concept nanorobots capable of early detection and destruction of infections, genome editing, and

smart therapeutic delivery, could be crucial in the fight against the disease [18]. In people with cardiovascular diseases, nanorobots can be used to identify and locate atherosclerotic lesions within the coronary artery. Also, they can be used to treat the same so that the blood flow can be brought back to normal [19].

5. Utilisation of Nanotherapeutics to Treat Cardiovascular Disorders

Several drugs like Nifedipine, Losartan, etc. can help to manage and treat cardiovascular complications. But the efficiency of the drug to work on the targeted artery is low as they are orally or systemically administered. Microscale instruments, used to open a blocked artery, are bulky and prone to infections. Nanotechnology offers a broad platform when it comes to cardiovascular science. Nanosensors like Quantum Dots (QDs) and nanocrystals can be used in this aspect. Nanomachines can be used in sensing, decision making and also carrying out the role. For example, Abciximab, a chimeric mouse-human monoclonal antibody, is a simple nanomachine in nature. It can help by reducing the chance of heart attacks in patients needing percutaneous coronary intervention [20].

Following are a few examples of nano-formulations which has shown promise against different cardiovascular diseases [21]:

- **Hypertension**
  Curcumin nanoemulsion, Carvedilol loaded solid-lipid nanoparticle, Nebivilol nanosuspensions
- **Hyperlipidemia**
  Curcumin, 17- βE and paclitaxel-loaded nanoemulsion
- **Stroke**
  Fullerene nanoparticles
- **Pulmonary Hypertension**
  Bosentan and NF-Kappa ¬β antagonists loaded nanoparticles
- **Myocardial Infarction**
  Nanoparticles with contrast agents for stem cell therapy, Irberrtan, and poly (lactic-co-glycolic) acid or PLGA nanoparticles
- **Thrombosis**
  Tissue plasminogen activator (tPA)-loaded PGLA nanoparticles exhibited therapeutic efficacy to dissolve blood clot in a very short time [22].

5.1. Role of Natural Products in the Treatment of Cardiovascular Disorders

Natural products play a significant role in the treatment of the cardiovascular disorder. It is effective as the side effects are less than inorganic medications. Dietary flavonoids like Eriodictyol, Hesperetin obtained from citrus fruits are known to lower the risk of ischaemic stroke. Theaflavins obtained from apples and grapes help to regulate blood pressure [23]. The polyphenols, epicatechin, quercetin, and rutin, extracted from motherwort and hawthorn, are cardioprotective [24]. Ginsenosides, the constituent of Ginseng, help to reduce cardiac injury through the ACE2 receptor found on the myocardium. Also, they reduce systemic inflammation which helps to ameliorate the damages caused by cytokine storm and protect cardiac muscle [25]. Other phytochemicals which showed strong cardioprotective potential against damages by COVID-19 are thymoquinone, nicotinamide, emodin, and osthole [26, 27]. These natural products can be easily used to treat the cardiac damages caused by viral infection.

6. Potential of Natural Product Derived Nanotherapeutics in Curing Cardiovascular Complications Associated with COVID-19

As mentioned before, nanotherapeutics has its application in the treatment and management of various cardiovascular alignments. Hence, the incorporation of natural products within the nanoformulation could be one of the ways to achieve therapeutic potential during cardiovascular damage during COVID-19 infection. For example,

resveratrol, a phytochemical, obtained from grapes and berries, is known to provide protection against vascular damages that are caused by cardiovascular diseases. But it has low oral bioavailability. Resveratrol loaded in PLGA nanoparticles have shown a significant increase in bioavailability. In a similar fashion, the degradation of the said compound can also be reduced by incorporating it within polymeric nanoparticles and therefore, the longevity of the formulation can be increased [28].

Another strategy that can be identified is the utilization of nanorobots for targeted drug delivery. As mentioned before, nanorobots can be used for increased efficiency when it comes to targeted drug delivery. For instance, ginsenosides can be loaded within nanoparticles that can be further loaded within the nanorobots. These nanorobots can unload the drug-containing nanoparticles near the ACE2 receptors near the myocardium. This can block the said receptors and therefore, the injury within the heart tissue can be stopped [25].

Table 1. Table containing examples of nanoformulation derived from natural products which show cardiovascular activity.

Name of the Natural Product	Source	Nanoformulations	Mechanism of action	Reference
Total flavonoid extract (tilianin, luteolin, and rosmarinic acid)	*Dracocephalum moldavica* L.	Solid lipid nanoparticle	Improves the integrity of myocardial membrane; reduces the level of IL-1β & TNF-α	29
Curcumin	*Curcumin longa*	Curcumin nanoemulsion	Increases 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition showing antihypercholestrolemic activity	30
Quercetin	*Prunus avium*	Quercetin-loaded PLGA	Reduces the production of the inflammatory cytokines	30
Ginsenoside R3	*Panax ginseng*	R3 loaded in Pluronic F127 micelles	Reduces myocardial levels of LDH, CK-MB, & CK. Maintains integrity of myocytes and reduces apoptosis	30
Berberine	*Berberis* spp.	Liposomal encapsulations containing berberine	In myocardial infraction, it preserves left ventricular ejection, reduces adverse cardiac remodeling	30

Resveratrol	-	Polycaprolactone encapsulated resveratrol nanocapsule	Reduces systolic and diastolic blood pressure	30
Resveratrol	-	Solid lipid nanoparticle loaded with Resveratrol	Protects heart from Doxorubicin-induced toxicity; increases heart rate, ejection fraction, and fractional shortening	31
Breviscapine	*Erigeron breviscapus*	Lipid emulsion	Removes blood stasis and promotes blood circulation	30, 32
Methanolic extract	*Syzygium cumini*	Silver nanoparticle	Reduces oxidative damage and maintains the integrity of high glucose stressed cardiac cells	33

7. Conclusion

COVID-19 caused by SARS-CoV-2 has the potential to cause a wide array of damage within the body. In worst-case scenarios, it can lead to multi-organ failure and finally death. The number of cardiac complications associated with the disease is huge which calls for immediate actions. Nanotechnology can be a good alternative to the traditional therapy that is most commonly provided to patients. So, the scientific and medical communities need to find ways to incorporate nanotechnology within their repertoire and make it commonly available for people.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix

Figure 1: Pathophysiology of COVID-19 adapted from [5].

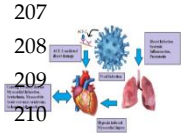

Figure 2: Probable cardiovascular complications associated with COVID-19 (adapted from [12]).

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