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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 medical 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, previously healthy patients have mostly developed cardiovascular diseases. Natural products can be used as a cure for 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

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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 such as 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 natural products that have the potential to cure cardiovascular alignments, followed by discussions on the role of nanotechnology in the pandemic and its potential to cure cardiovascular complications. 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 hosts. 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 individuals show clinical symptoms within 2 to 14 days of exposure to the virus [4]. The pathophysiology is detailed in Figure 1.

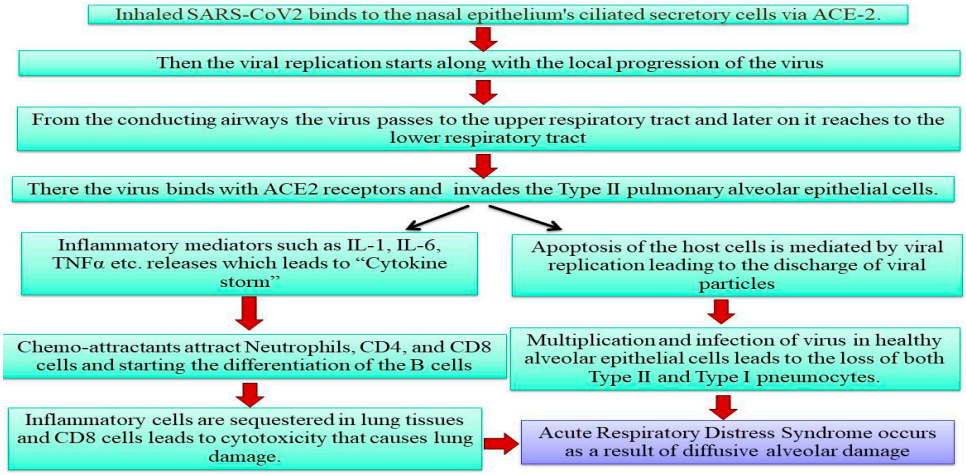

Figure 1. Pathophysiology of COVID-19 (Adapted from Ref. [5]).

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 a "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 are 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 damage caused by the virus [6,10].

Other than the major organs, the constituents of human blood are also altered due to COVID-19. As mentioned before, there is a hyperinflammatory response of the body due to the infection. The count of platelets decreases and fibrin degradation products or D-dimers 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 issue 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 complications have affected not only individuals with pre-existing cardiovascular issues but also 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 myocytes causes damage in the heart but the exact pathophysiology of the same is not clearly known [12]. 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, oxygen demand is never met, which translates to damage [12]. The pathophysiology is further described in Figure 2. The initial stages of the viral infection sometimes show malfunction of the respiratory system and in the later stages, the cardiac complications are more

pronounced. Other than that, arrhythmias (tachycardia, bradycardia, and asystole) are a common part of cardiovascular complications associated with COVID-19 infections [6].

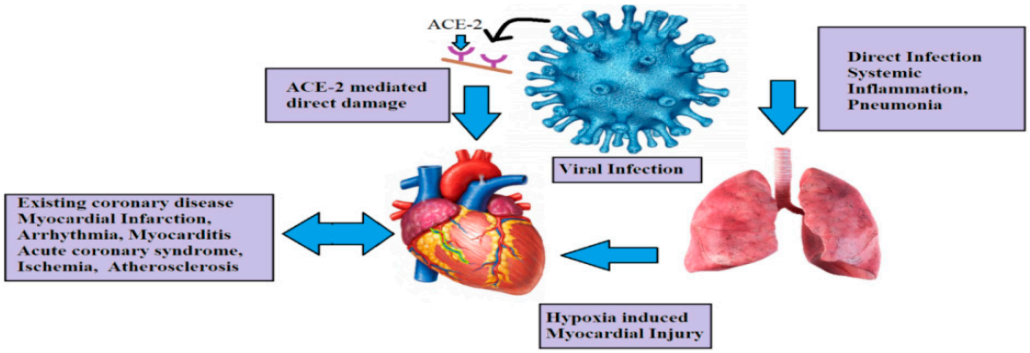

Figure 2. Probable cardiovascular complications associated with COVID-19 (Adapted from Ref. [12]).

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 diagnostic tools that are 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 (such as the 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 of merging vaccination and nanotechnology. Encapsulation of the viral genome can do the work of vaccination without any significant side effects. Pfizer-BioNTech has developed one such vaccine incorporating mRNA within liposomal nanoparticles or PEGylated liposomes (BNT162b). 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 systemic inflammation [15].

There are no standardized treatment protocols available to treat the clinical manifestations associated with COVID-19. However, based on previous experiments, probable treatments can be obtained. For instance, pulmonary fibrosis is a very common effect of viral infection. 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 of 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. In addition, 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 such as Nifedipine, Losartan, etc. can help to manage and treat cardiovascular complications. However, the efficacy of the drug in working 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 such as 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 nanoparticles; nebivilol nanosuspensions.

- **Hyperlipidemia**

  Curcumin; 17- βE and paclitaxel-loaded nanoemulsion.

- **Stroke**

  Fullerene nanoparticles.

- **Pulmonary Hypertension**

  Bosentan and NF-Kappa ¬β antagonist 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 clots in a very short time [22].

Role of Natural Products in the Treatment of Cardiovascular Disorders

Natural products play a significant role in the treatment of cardiovascular disorders. They are effective as their side effects are less than those of inorganic medications. Dietary flavonoids such as eriodictyol and 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 constituents of ginseng, help to reduce cardiac injury through the ACE2 receptor found on the myocardium. Furthermore, they reduce systemic inflammation, which helps to ameliorate the damage caused by cytokine storms 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 damage caused by viral infection.

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

As mentioned before, nanotherapeutics has applications in the treatment and management of various cardiovascular disorders. Hence, the incorporation of natural products within nanoformulations could be one way to achieve therapeutic potential for cardiovascular damage during COVID-19 infection. For example, resveratrol, a phytochemical, obtained from grapes and berries, is known to provide protection against vascular damage caused by cardiovascular diseases. However, it has low oral bioavailability, and resveratrol

loaded in PLGA nanoparticles has 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]. The examples of a few of such nanoformulations have been presented in Table 1. From the data of the table it can be seen that natural products (extracts or isolated compounds) have been incorporated within nanoformulations for which the resultant product shows better therapeutic efficacy.

Table 1. Table containing examples of nanoformulations derived from natural products that 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, and CK. Maintains integrity of myocytes and reduces apoptosis	[30]
Resveratrol	-	Liposomal encapsulations containing berberine	In myocardial infraction, it preserves left ventricular ejection and reduces adverse cardiac remodeling	[30]
Resveratrol	-	Polycaprolactone encapsulated resveratrol nanocapsule	Reduces systolic and diastolic blood pressure	[30]
		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]

Another strategy that can be identified is the utilization of nanorobots for targeted drug delivery. As mentioned before, nanorobots can be used for increased efficacy 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].

7. Conclusions

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. Thus, the scientific and medical communities need to find ways to incorporate nanotechnology into their repertoires and make it widely available for patients.

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References

1. Yuki, K.; Fujiogi, M.; Koutsogiannaki, S. COVID-19 pathophysiology: A review. *J. Clin. Immunol.* **2020**, *215*, 108427. [CrossRef] [PubMed]
2. Lotfi, M.; Hamblin, M.R.; Rezaei, N. COVID-19: Transmission, prevention, and potential therapeutic opportunities. *Clin. Chim. Acta* **2020**, *508*, 254–266. [CrossRef] [PubMed]
3. Nalbandian, A.; Sehgal, K.; Gupta, A.; Madhavan, M.V.; McGroder, C.; Stevens, J.S.; Cook, J.R.; Nordvig, A.S.; Shalev, D.; Sehrawat, T.S.; et al. Post-acute COVID-19 syndrome. *Nat. Med.* **2021**, *27*, 601–615. [CrossRef]
4. Malone, R.W.; Tisdall, P.; Fremont-Smith, P.; Liu, Y.; Huang, X.P.; White, K.M.; Miorin, L.; Moreno, E.; Alon, A.; Delaforge, E.; et al. COVID-19: Famotidine, histamine, mast cells, and mechanisms. *Front. Pharmacol.* **2021**, *12*, 633680. [CrossRef] [PubMed]
5. Parasher, A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. *Postgrad. Med. J.* **2021**, *97*, 312–320. [CrossRef] [PubMed]
6. Jain, U. Effect of COVID-19 on the Organs. *Cureus* **2020**, *12*, e9540. [CrossRef] [PubMed]
7. Nuzzo, D.; Picone, P. Potential neurological effects of severe COVID-19 infection. *J. Neurosci. Res.* **2020**, *158*, 1–5. [CrossRef] [PubMed]
8. Higgins, V.; Sohaei, D.; Diamandis, E.P.; Prassas, I. COVID-19: From an acute to chronic disease? Potential long-term health consequences. *Crit. Rev. Clin. Lab. Sci.* **2021**, *58*, 297–310. [CrossRef]
9. Bzeizi, K.; Abdulla, M.; Mohammed, N.; Alqamish, J.; Jamshidi, N.; Broering, D. Effect of COVID-19 on liver abnormalities: A systematic review and meta-analysis. *Sci. Rep.* **2021**, *11*, 10599. [CrossRef]
10. Kaafarani, H.M.; El Moheb, M.; Hwabejire, J.O.; Naar, L.; Christensen, M.A.; Breen, K.; Gaitanidis, A.; Alser, O.; Mashbari, H.; Bankhead-Kendall, B.; et al. Gastrointestinal complications in critically ill patients with COVID-19. *Ann. Surg.* **2020**, *272*, e61. [CrossRef]
11. Merad, M.; Martin, J.C. Pathological inflammation in patients with COVID-19: A key role for monocytes and macrophages. *Nat. Rev. Immunol.* **2020**, *20*, 355–362. [CrossRef] [PubMed]
12. Tan, W.; Aboulhosn, J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. *Int. J. Cardiol.* **2020**, *309*, 70–77. [CrossRef] [PubMed]
13. Aghagoli, G.; Gallo Marin, B.; Soliman, L.B.; Sellke, F.W. Cardiac involvement in COVID-19 patients: Risk factors, predictors, and complications: A review. *J. Card. Surg.* **2020**, *35*, 1302–1305. [CrossRef] [PubMed]
14. Krishnan, S.; Narasimhan, A.K.; Gangodkar, D.; Dhanasekaran, S.; Jha, N.K.; Dua, K.; Thakur, V.K.; Gupta, P.K. Aptameric nanobiosensors for the diagnosis of COVID-19: An update. *Mater. Lett.* **2022**, *308*, 131237. [CrossRef] [PubMed]
15. Dube, T.; Ghosh, A.; Mishra, J.; Kompella, U.B.; Panda, J.J. Repurposed drugs, molecular vaccines, immune-modulators, and nanotherapeutics to treat and prevent COVID-19 associated with SARS-CoV-2, a deadly nanovector. *Adv. Ther.* **2021**, *4*, 2000172. [CrossRef] [PubMed]
16. Abdel-Bakky, M.S.; Amin, E.; Ewees, M.G.; Mahmoud, N.I.; Mohammed, H.A.; Altowayan, W.M.; Abdellatif, A.A. Coagulation System Activation for Targeting of COVID-19: Insights into Anticoagulants, Vaccine-Loaded Nanoparticles, and Hypercoagulability in COVID-19 Vaccines. *Viruses* **2022**, *14*, 228. [CrossRef]
17. Liu, L.; Ren, J.; He, Z.; Men, K.; Mao, Y.; Ye, T.; Chen, H.; Li, L.; Xu, B.; Wei, Y.; et al. Cholesterol-modified hydroxychloroquine-loaded nanocarriers in bleomycin-induced pulmonary fibrosis. *Sci. Rep.* **2017**, *7*, 10737. [CrossRef]

18. Hassanzadeh, P. Nanotheranostics against COVID-19: From multivalent to immune-targeted materials. *J. Control. Release* **2020**, *328*, 112–126. [CrossRef]
19. Cavalcanti, A.; Rosen, L.; Kretly, L.C.; Rosenfeld, M.; Einav, S. Nanorobotic challenges in biomedical applications, design and control. In Proceedings of the 2004 11th IEEE International Conference on Electronics, Circuits and Systems, Tel Aviv, Israel, 13–15 December 2004; IEEE: Piscataway, NJ, USA; pp. 447–450. [CrossRef]
20. Sahoo, S.K.; Parveen, S.; Panda, J.J. The present and future of nanotechnology in human health care. *Nanomedicine.* **2007**, *3*, 20–31. [CrossRef]
21. Martín Giménez, V.M.; Kassuha, D.E.; Manucha, W. Nanomedicine applied to cardiovascular diseases: Latest developments. *Ther. Adv. Cardiovasc. Dis.* **2017**, *11*, 133–142. [CrossRef]
22. Korin, N.; Kanapathipillai, M.; Matthews, B.D.; Crescente, M.; Brill, A.; Mammoto, T.; Ghosh, K.; Jurek, S.; Bencherif, S.A.; Bhatta, D.; et al. Shear-activated nanotherapeutics for drug targeting to obstructed blood vessels. *Science* **2012**, *337*, 738–742. [CrossRef] [PubMed]
23. Khan, J.; Deb, P.K.; Priya, S.; Medina, K.D.; Devi, R.; Walode, S.G.; Rudrapal, M. Dietary flavonoids: Cardioprotective potential with antioxidant effects and their pharmacokinetic, toxicological and therapeutic concerns. *Molecules* **2021**, *26*, 4021. [CrossRef] [PubMed]
24. Arbeláez, L.F.; Pardo, A.C.; Fantinelli, J.C.; Schinella, G.R.; Mosca, S.M.; Ríos, J.L. Cardioprotection and natural polyphenols: An update of clinical and experimental studies. *Food Funct.* **2018**, *9*, 6129–6145. [CrossRef] [PubMed]
25. Hossain, M.A.; Kim, J.H. Possibility as role of ginseng and ginsenosides on inhibiting the heart disease of COVID-19: A systematic review. *J. Ginseng Res.* **2022**, *46*, 321–330. [CrossRef] [PubMed]
26. Ahmad, A.; Raish, M.; Alkharfy, K.M. The potential role of thymoquinone in preventing the cardiovascular complications of COVID-19. *Curr. Vasc. Pharmacol.* **2021**, *141*, 106899. [CrossRef]
27. Abubakar, M.B.; Usman, D.; Batiha, G.E.; Cruz-Martins, N.; Malami, I.; Ibrahim, K.G.; Abubakar, B.; Bello, M.B.; Muhammad, A.; Gan, S.H.; et al. Natural products modulating Angiotensin Converting Enzyme 2 (ACE2) as potential COVID-19 therapies. *Front. Pharmacol.* **2021**, *12*, 1–19. [CrossRef]
28. Pechanova, O.; Dayar, E.; Cebova, M. Therapeutic potential of polyphenols-loaded polymeric nanoparticles in cardiovascular system. *Molecules* **2020**, *25*, 3322. [CrossRef]
29. Tan, M.E.; He, C.H.; Jiang, W.; Zeng, C.; Yu, N.; Huang, W.; Gao, Z.G.; Xing, J.G. Development of solid lipid nanoparticles containing total flavonoid extract from Dracocephalum moldavica L. and their therapeutic effect against myocardial ischemia–reperfusion injury in rats. *Int. J. Nanomed.* **2017**, *12*, 3253. [CrossRef]
30. Hesari, M.; Mohammadi, P.; Khademi, F.; Shackebaei, D.; Momtaz, S.; Moasefi, N.; Farzaei, M.H.; Abdollahi, M. Current Advances in the use of nanophytomedicine therapies for human cardiovascular diseases. *Int. J. Nanomed.* **2021**, *16*, 3293–3315. [CrossRef]
31. Zhang, L.; Zhu, K.; Zeng, H.; Zhang, J.; Pu, Y.; Wang, Z.; Zhang, T.; Wang, B. Resveratrol solid lipid nanoparticles to trigger credible inhibition of doxorubicin cardiotoxicity. *Int. J. Nanomed.* **2019**, *14*, 6061–6071. [CrossRef]
32. Xiong, F.; Wang, H.; Geng, K.K.; Gu, N.; Zhu, J.B. Optimized preparation, characterization and biodistribution in heart of breviscapine lipid emulsion. *Chem. Pharm. Bull.* **2010**, *58*, 1455–1460. [CrossRef] [PubMed]
33. Atale, N.; Saxena, S.; Nirmala, J.G.; Narendhirakannan, R.T.; Mohanty, S.; Rani, V. Synthesis and characterization of Sygyzium cumini nanoparticles for its protective potential in high glucose-induced cardiac stress: A green approach. *App. Biochem. Biotechnol.* **2017**, *181*, 1140–1154. [CrossRef] [PubMed]