COVID 19: Resveratrol as a Potential Supplement to Mitigate the Cardiotoxicity Associated with Chloroquine and Hydroxychloroquine Treatment

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Abstract: The challenges of SARS-CoV-2 have frightened the world due to a lack of effective treatment. Many clinicians have adopted drug repositioning because of the urgent need to contain the viral pandemic. Several studies have demonstrated the *in vitro* and *in vivo* antiviral efficacy of chloroquine and hydroxychloroquine in the treatment of SARS-CoV-2. However, the cardiovascular toxicity of chloroquine and hydroxychloroquine stand as a limitation to their general use to treat SARS-CoV-2. Thus, it is necessitated the search for an adjuvant that could be used alongside these treatments to mitigate the undesired effect. The cardioprotective activity of resveratrol could serve to mitigate the cardiovascular toxicity of chloroquine and hydroxychloroquine. Its antioxidant and anti-inflammatory properties synergistically with chloroquine or hydroxychloroquine could also mitigate the antiviral activity of SARS-CoV-2. In this review, we explore chloroquine and hydroxychloroquine for SARS-CoV-2 treatment and suggest their synergetic use with resveratrol as a recommended therapy to mitigate cardiovascular toxicity and contribute to their antiviral effects.

Keywords: natural products; drug repurposing; treatment strategies; Covid-19; antiviral; toxicity.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an important human and animal viral infection that has frightened the world due to a lack of effective treatment [1]. It can cross species barriers with newly emerged properties, causing novel and fatal diseases [2]. Lack of effective therapy against SARS-CoV-2 has led clinicians to drug repositioning using existing antiviral and antimalarial drugs to limit the severity and treat SARS-CoV-2 [3]. The antimalarial drug, chloroquine, and analog hydroxychloroquine have been proven to exhibit antiviral properties and effectively treat autoimmune diseases. However, these drugs can have cardiovascular adverse effects and decrease nasopharyngeal viral load, which could be an exposure mechanism to ventricular arrhythmias [4]. On the other side, resveratrol and its analogs have shown antiviral effects against respiratory infections [6] and possess cardioprotective effects, which are enhanced by its antioxidant and anti-inflammatory activities. Although clinical evidence to support this is minimal, there is contrasting evidence pointing to their potential safety [5]. However, there is an urgent demand to produce effective therapy for SARS-CoV-2 treatment. Drug repositioning with a known safety profile and side effects might be effective. This review aims to explore the use of chloroquine and

hydroxychloroquine with resveratrol to mitigate the adverse cardiotoxicity induced by chloroquine and hydroxychloroquine and recommend it as a treatment measure for SARS-CoV-2 with supporting data of *in vitro*, *in vivo*, and clinical trials.

2. Chloroquine and Hydroxychloroquine

Chloroquine and its analog, hydroxychloroquine, are widely available old drugs used in treating malaria and autoimmune diseases [1,7]. However, its excellent anti-inflammatory and immunoregulatory properties are quite surprising to medical experts. Both compounds can inhibit proteolytic processes, acidification of endosomal cells, and glycosylation of host receptors, thereby blocking the viral entry into the cells [8]. They also inhibit lysosomal activities, autophagy, and the synthesis of pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interferon-γ (IFN-γ) in the host cells [9]. The replication of SARS-CoVs in cells results in pulmonary endothelial and epithelial cells' injury, causing an inflammatory increase of cytokines in the plasma. The anti-inflammatory and immunoregulatory property chloroquine and hydroxychloroquine pose labeled them as a "game-changer" with the possibility of attenuating the inflammatory response and replication of SARS-CoVs [8]. Chloroquine and hydroxychloroquine mediated inhibition of SARS-CoVs by inhibiting pro-inflammatory cytokines and markers using *in vitro* studies of peripheral blood mononuclear cells has been well established [8]. *In vivo* study, using mice has demonstrated that these compounds have some activity against the human SARS-CoV virus [8]. A clinical trial was carried out on hydroxychloroquine by Gautret, and his coworkers show a reduction/clearance in the viral load of SARS-CoV-2 patients. However, it has a limitation of the small sample size [10]. These compounds have shown *in vitro* activities against several viruses [1]; however, the results obtained against the SARS-CoV-2 virus were more promising compared to other viral disease trials [8]. A great limitation to some of the evidence is that there is no high-quality way to ascertain the efficacy of these compounds in treating viral infection.

3. Mechanism of Action Against Viral Infections

The mechanisms of action of hydroxychloroquine and chloroquine are closely related because hydroxychloroquine is an analog of chloroquine. The mechanism of action is not clearly understood as many studies have revealed different mechanisms. Both compounds can prevent viral entry in the cell and also stop post-entry events [8]. Chloroquine stops viral entry by inhibiting the enzyme quinone reductase II, an enzyme required to synthesize sialic acid in the body [11]. During viral capsid injection into the cell, sialic acid is important for the viral attachment to the cell [12]. Studies have also shown that chloroquine and hydroxychloroquine interfere with angiotensin-converting enzyme 2 receptor (ACE2) glycosylation by preventing the virus from entering the cells [13,14]. SARS-CoV-2 has also been proven to use this mechanism for its replication in the cell. It also fuses with the endosomal membrane in an acidic medium in the lysosome, thereby uncoating itself and releasing its content into the cell [15]. Chloroquine can increase the pH of endosomes and therefore interfere with virus replication in its early stage. Hydroxychloroquine also increases endosomal pH and interfere with toll-like-receptor signaling important in the transcription of pro-inflammatory genes [14]. Chloroquine hinders the degradation of lysosomal protein and its fusion with autophagosomes [16,17]. *In vitro* studies also prove that chloroquine is anti-autophagy via its cytotoxic effect

on cells [18]. It also interferes with proteolytic processes via the impairment of posttranslational modification of viral protein [19]. Both compounds are anti-inflammatory agents; they reduce tumor necrosis factor (TNFα) released during trauma and infection [20]. Hydroxychloroquine inhibits T-cells activation and the expression of CD145 via hindering the major histocompatibility complex (MCH) class II expression [21,22]. Both drugs' ability to work via a multi-target mechanism raised the interest of using them to treat SARS-CoV-2.

4. Chloroquine and Hydroxychloroquine Versus SARS-CoV-2 (*In vitro*)

In vitro studies have shown antiviral chloroquine and hydroxychloroquine activities before the onset of 2019 SARS-Cov-2 [8]. Both compounds inhibit a diverse range of CoVs and non CoVs virus replication [2]. However, the table below summarizes the activities of chloroquine and hydroxychloroquine versus SARS-CoV-2 *in vitro*.

Table 1. *In vitro* activity of chloroquine and hydroxychloroquine against SARS-CoV-2.

Drug	Experimental Design	Experimental Outcome	EC_{50} (μM)	Reference
Chloroquine	Infected Vero E6 cell culture with SARS-CoV-2 at Multiplicity of infection (MOI) of 0.05 and treated with a varying dosage of the drug	Reduction in viral replication. Highly effective, especially when combined with Remdesivir to treat SARS-CoV-2	1.13	[23]
Chloroquine	Vero E6 cells infected with SARS-CoV-2 (MOI of 0.01) and treated at varying dosage of 0.032, 0.16, 0.80, 4, 20, 100 μM for 24 or 48 hours	Reduction in the replication of the virus With an EC_{50} value of 5.47 μM after 48h of incubation	5.47	[24]
Chloroquine	Infected Vero E6 cell culture with SARS-CoV-2 at varying MOIs of 0.01, 0.02, 0.2, and 0.8 at a varying dosage of 2.71, 3.81, 7.14, and 7.36 μM	Reduction in viral replication	2.71–7.36	[4]
Hydroxychloroquine	Vero E6 cells were infected with SARS-CoV-2 at MOI of 0.01 and treated at varying dosage of 0.032, 0.16, 0.80, 4, 20, 100 μM for 24 or 48 hours	Reduction in viral replication	0.72	[24]
Hydroxychloroquine	SARS-CoV-2 infected Vero E6 cell culture at varying dosage of (4.51, 4.06, 17.31, and 12.96 μM	Reduction in viral replication	4.06–17.31	[4]

An experiment carried out by Wang and his coworkers using infected Vero E6 cells with SARS-CoV-2 multiplicity of infections (MOIs) 0.05 showed that chloroquine could inhibit the viral replication and was more effective when combined with remdesivir [23]. Also, chloroquine and hydroxychloroquine at varying dosage reduce viral replication with an EC50 of 5.47 μM and 0.72 μM, respectively. In the experiment carried out by Yao and his coworkers, hydroxychloroquine was more effective than chloroquine against SARS-CoV-2 [24]. The MOI of SARS-Cov-2 was varied by Liu and his coworkers with a varying dosage of chloroquine and hydroxychloroquine to treat the infected cells. Both drugs were active against SARS-CoV-2 by reducing viral replication; however, in contrast to the experiment carried out by Wang and coworkers, chloroquine was more effective than hydroxychloroquine, having an EC50 between 2.71 μM and 7.36 μM [4]. The interpretation of these findings is that chloroquine and its analog hydroxychloroquine are capable of attenuating SARS-CoV-2 *in vitro*.

5. *In vivo* Activities of Chloroquine Against SARS-CoVs

The data available for the *in vivo* antiviral activities of chloroquine against the SARS-CoVs viruses are limited. There is no reported data on *in vivo* study of hydroxychloroquine against SARS-CoVs. The present study showed no significant chloroquine activities against SARS-CoVs; however, it significantly reduced HCoV-OC43 replication in mice [25] and increased the fetus survival rate of infected mice [26].

Table 2. *In vivo* activity of Chloroquine against SARS-CoV-2.

Drug	Experimental Design	Dosage	Experimental Outcome	Reference
Chloroquine	Intraperitoneal or intranasal administration of SARS-CoV in mice	1-50mg/d	Tolerated but ineffective	[27]
Chloroquine	Subcutaneous administration of HCoV-OC43 in mice	15mg/d	Effective	[25]
Chloroquine	Subcutaneous administration of HCoV-OC43 in mice	30mg/d then 15mg/d	effective	[26]
Chloroquine	Subcutaneous administration of FIPV in cat	10mg/3days	No significant effect	[28]

6. Chloroquine and Hydroxychloroquine Versus SARS-CoV-2: Clinical Trials

Available clinical trials to understand the effectiveness of chloroquine and hydroxychloroquine treatment against SARS-CoV-2 infected patients are very limited (Table 3). Some evidence has shown a significant benefit of using chloroquine and hydroxychloroquine in SARS-CoV-2 treatment; however, it must be stated that these shreds of evidence have significant limitations like small sample size and appropriate statistical presentation, which cannot be overlooked.

Table 3. *In vivo* clinical trials of Chloroquine and hydroxychloroquine against SARS-CoV-2.

Drug	Experimental Design	Dosage	Reported Severity of Infection	Experimental Outcome	Reference
Hydroxychloroquine	Uncontrolled noncomparative open-label observational study on 80 patients	200mg of HCQ trice daily for 10days + 500mg AZ on day 1 followed by 250mg /day from the 4th day	Mild illness	Clinical improvement with reduction in nasopharyngeal viral load. 83% of the patients had a negative viral culture at the end of the 7th day.	[10]
Hydroxychloroquine	Open labeled randomize parallel-group trial on 62 patients	200mg of HCQ twice daily	Moderate illness	Significant clinical improvement on cough, body temperature, and pneumonia. 3.2% of the patients had mild adverse reactions of rash and headache to HCQ.	[29]
Hydroxychloroquine	Controlled randomized open-label trial on 30 patients	200mg of HCQ twice daily	Mild illness	No statistically significant difference in clinical outcomes between the two groups	[30]
Hydroxychloroquine	Uncontrolled noncomparative open-label	600mg of HCQ per day for 10days + 500mg	Moderate illness	80% of the patient had positive SARS-CoV-2 in their RNA at day 5 &	[31]

Drug	Experimental Design	Dosage	Reported Severity of Infection	Experimental Outcome	Reference
	observational study on 11 patients	AZ on day 1 followed by 250mg /day from day 2-5		6 after treatment initiation	
Hydroxychloroquine	A longitudinal cohort study on 807 patients	Dosages not available	Moderate illness	No reduction in mortality rate or need for mechanical ventilation in groups with HCQ treatment.	[32]
Hydroxychloroquine	A longitudinal cohort study on 181 patients	600mg of HCQ per day for 48hours after admission	Moderate illness	No reduction in the number of deaths and acute respiratory distress syndrome within 7 days.	[33]
Hydroxychloroquine	Uncontrolled noncomparative observational study on 1061 patients	200mg of HCQ trice daily for 10days + 500mg AZ on day 1 followed by 250mg /day from the 4th day	Mild illness	Significant reduction in mortality rate compared with patients under different regiments from other hospitals.	[34]
Hydroxychloroquine	A longitudinal cohort study on 63 patients	Dosages not available	Moderate illness	Significant improvement in respiratory status with no significant difference in the mortality rate, therefore no significant clinical efficacy.	[35]
Hydroxychloroquine	Randomized open-label control study on 150 patients	1200mg of HCQ per day for 3 days followed by 300mg per day for 2 weeks in mild-moderate patients or 3 weeks in severe patients	Mild-moderate illness	No significant higher negative conversion was observed. Adverse drug reaction was observed in two of the patients.	[36]
Chloroquine	Randomized double-blinded safety-oriented study on 81 patients	High dose: 600mg twice daily for 10 days Low dose: 450mg twice on day 1 and once daily for 4 days	Moderate illness	50% reduction in lethality as compared to a low dose group; therefore high dosage is not recommended for use. No significant difference in clinical improvement.	[37]
Hydroxychloroquine	Safety oriented longitudinal cohort study on 84 patients	Dosage not available	Moderate-severe illness	It shows an increase in QT interval prolongation, drug-induced torsades de pointes (TdP), and drug-induced-sudden cardiac death (SCD).	[38]
Hydroxychloroquine	Non-randomized open-label study on 36 patients	600mg per day for 10 days	Moderate illness	There was a significant reduction in the viral load of patients receiving HCQ only at day 6 and negative SARS-CoV-2 test in all six patients that received a combination of HCQ and AZT.	[10]
Chloroquine	Interim study on 100 patients from 10 hospitals	Not reported	Not applicable	Chloroquine more superior to control in promoting a virus-negative conversion and shortening the	[39]

Drug	Experimental Design	Dosage	Reported Severity of Infection	Experimental Outcome	Reference
				disease course with no adverse effect.	

An experiment carried out by Gautret, and his coworkers showed that 600mg of hydroxychloroquine for ten days lessen the viral load of the patient who received the medication. The combined use of hydroxychloroquine with azithromycin completely cleared SARS-CoV-2 in all six patients that received the medication [10]. Gautret *et al.* [10] also carried out another experiment on 80 hospitalized using the combination of hydroxychloroquine and azithromycin, 83% had an undetectable viral load on day seven, and 81% of the patients survived to hospital discharge [10]. Molina *et al.* also carried out a longitudinal cohort study on 11 patients using the same dosage as Gautret *et al.*. The result shows that 80% still had SARS-CoV-2 RNA in their nasopharyngeal swap, which is in contrast to Gautret *et al.* observation [40]. Chen *et al.* experiment on 62 patients using 200mg of hydroxychloroquine twice daily showed significant clinical improvement on cough, body temperature, and pneumonia; however, 2 of the patients had an adverse reaction of rash and headache [29]. Million *et al.*'s experiment showed that there is a significant mortality reduction in 1061 SARS-CoV-2 patients using a combination of hydroxychloroquine and azithromycin [34]. Borba *et al.* compared a high dosage of chloroquine (600mg) with a low dosage (450mg) on 81 patients and found out 50% reduction in lethality as compared with a low dosage; however, no significant clinical difference between both dosages [37]. Gao *et al.* carried out an interim report on 100 patients. They stated that chloroquine is more superior to control in promoting a virus-negative conversion and shortening the disease course with no adverse effect [39]. Some other experiments carried out on hydroxychloroquine also showed no significant improvement in SARS-CoV-2 patients [29,33,36].

These reports have a common limitation of small sample size, many are not a peered-reviewed article. They have reported different outcomes using the same drug and similar dosage (inconsistency in their results), and therefore these reports should be treated as a sole hypothesis.

7. Contraindication and Adverse Effect of Chloroquine and Hydroxychloroquine

The possible efficacy of chloroquine and its analog hydroxychloroquine as a therapy against SARS-CoV-2 has been proven to be associated with adverse cardiovascular toxicity [23,39,40]. These drugs' cardiovascular effect involves cardiac arrhythmias, changes in the electrical conductivity of the myocardium [41-43], and myocardial hypertrophy, a structural change in the entire myocardium. The fundamental mechanism of chloroquine and hydroxychloroquine in cardiovascular toxicity is autophagy inhibition [44,45], which is antiarrhythmic or proarrhythmic depending on the elementary condition [46,47].

The common hypersensitivity to chloroquine and hydroxychloroquine is abdominal discomfort and nausea [48]. Retinal field changes might occur due to the binding of the drugs to melanin, damaging the cornea and retina [49]. According to some reports, hydroxychloroquine has been safer and less toxic than chloroquine; however, this lacks substantial evidence [20]. The chances of experiencing some of these side effects are low in adults except in elderly patients [2]. A report showed that side effects would only be seen if the drug is continually used for 5 years at a dosage of 6.5mg/kg/d [50]. Co-administration of chloroquine and hydroxychloroquine with other drugs might also increase the risk of its side

effect. The combined use of hydroxychloroquine and azithromycin might prolong the QTc interval, according to Gautret *et al*. [10]. There are few cases of both drugs causing a life-threatening disease, cardiomyopathy, since both drugs can prolong QTc [51,52]. Other toxicities associated with hydroxychloroquine that is less reported include ototoxicity and urticarial [53].

The cell's inability to degrade and recirculate the heart's cellular components results in accelerated cell damage and ischemia-reperfusion injury, causing a change in autophagic flux and aggravated cell death mechanism [54-56]. The inhibition of different ion channels plays an opposite and different role in myocardial death. The blockage of Na^+ and K^+ might be responsible for intraventricular blockage with multiple bundle branches and prolonged action potential time, respectively. In contrast, the cell exhibits a protective mechanism by inhibiting Na^+ and Ca^{2+} load to oppose myocardial death [57]. The contrasting balanced activity of various ion channels might be responsible for limited prolonged QT interval in low and moderate dosage for a short time. Chloroquine affects the QRS complex's dilation and causes arrhythmia in the cardiac muscles when it binds to Na^+, K^+, and Ca^{2+} ions. These drugs' effect is dose-dependent [58]; the rhythmic changes in the heart are reversible when the drug is withdrawn.

Cardiomyopathy, however, is irreversible, but the treatment must have been for months before the onset of its effect. Some essential questions need an urgent answer when considering chloroquine and hydroxychloroquine as SARS-CoV-2 treatment due to their cardiac toxicity and the possibility of eliciting different mechanisms of toxicity. How to proceed with the usage of these drugs in the treatment of SARS-CoV-2? Is it wise to synergistically combine them with other potential drugs knowing that its cardiovascular toxicity mechanism depends on the underlying elementary condition? How can we supplement the drug to reduce the cardiotoxicity effect? Available reports show that the data available on randomized clinical trials are not significant enough to prove the effective dosage of the drugs and their time of use in the treatment of SARS-CoV-2. These quinolones' potential clinical benefit is significant to their toxicity because cardiac toxicity starts developing after the prolonged use of the drug at a high dose. Adverse drug reactions and prolonged QT intervals in some patients might be due to a good underlying ailment like diabetic patients and patients with electrolyte disorders. A baseline electrocardiogram should be checked on patients and their possible exclusion before the onset of the trial. Since the potential benefit of chloroquine and hydroxychloroquine supersedes its mild and tolerable side effect, it will be wise and thoughtful not to jeopardize a patient's life and consider these drugs to treat SARS-CoV-2, putting in mind the important questions for a better clinical outcome [59].

8. Resveratrol as a Potential Supplement with Chloroquine and Hydroxychloroquine

The use of natural products has been widely accepted throughout the history of disease prevention and treatment. Among such products available is resveratrol, which has been noted to play a major role in disease treatment via its potent defensive antioxidant. Resveratrol (3,4′,5- trihydroxystilbene) from the stilbene family (phenolic compounds) with two benzene rings linked via isopropyl moiety. Cis- and trans- forms (Z and E) stereoisomers of resveratrol exist. The E form has been implicated for the antioxidant and anticancer potential of the product. Resveratrol is a naturally occurring phytoalexin that was initially isolated in *Veratrum grandiflorum* in 1940. Resveratrol is well distributed in plant families such as *Vitaceae*,

Leguminosae, *Cyperaceae*, *Gnetaceae*, Dipterocarpaceae, and other food products, including grapes and blue, peanuts, cranberry juice, wine, cranberries, and mulberries. Under acidic conditions, it is poorly soluble in water [60].

Reports have shown that resveratrol has poor bioavailability and rapid metabolism, limiting its use as a drug. To improve its therapeutic effects, there will be increased oral dose administration [61]. Resveratrol intake in humans has shown to be a well-tolerated compound. However, at a concentration of more than 1 g/Kg, it produces side effects such as diarrhea, abdominal pain, and nausea [62].

Different effects of resveratrol include cardioprotective, antioxidant, anti-microbial, and anticancer properties [63]. However, several studies have attributed the antioxidant and anti-inflammatory properties of resveratrol about its cardioprotective activities [64-66]. Clinical trials of resveratrol administration (20 mg/day and 350 mg/day for 2 months and 6 months, respectively) significantly improved the inflammatory state in patients with high cardiovascular risk or diseases [67].

However, *in vitro* resveratrol studies revealed several cardioprotective properties due to its multiple molecular targets interaction [65,68]. Resveratrol restores ROS/antioxidant balance and counters the damages induced by oxidative stress, hence reveal its antioxidant properties [69]. Meng *et al.* [70] revealed that resveratrol also attenuates the inflammatory response and contributes to its cardioprotective effects. Schwager *et al.* [71] revealed that at 6.25–50 μM, resveratrol modulated the immune and endothelial cells to protect against inflammation via cytokine and chemokine profiles. For example, resveratrol suppressed NF-κB and upregulated sirtuin-1 [72].

The anticancer activity of resveratrol potentially protects against the initiation and progression of the tumor [70]. In different human tumor cell lines, resveratrol's anticancer activity was attributed mostly to apoptosis induction through the direct caspase cascade activation of anti-apoptotic pathways inhibition [73].

Resveratrol was noted as an antifungal and antibacterial agent. Resveratrol had shown to inhibit Gram-positive pathogens and Gram-negative pathogens at MIC 100–200 μg/ml and MIC greater than 200 μg/ml, respectively [63]. Euba et al*et al.* [74] revealed that 150 mg/kg resveratrol administered orally decreased the bacterial burden significantly in lung tissue with respiratory infection of Haemophilus influenza.

Presently, SARS-CoV-2, emerging respiratory viruses, have no drug to prevent or treat it. Hence, alternative potential treatment options are being explored to enhance disease management due to the scarce antiviral therapies and the disease's pathological complexity. A natural compound such as resveratrol should have been considered due to its therapeutic potential in several respiratory viral infections. Resveratrol and its analogs have been reported to show antiviral effects against respiratory infections such as influenza viruses, respiratory syncytial virus, coronavirus, metapneumovirus, and rhinovirus by directly inhibiting the viral replication and/or host immune response modulation [6]. The antioxidant, anti-inflammatory properties, and underlying cardioprotective resveratrol activities could help manage the various symptoms associated with respiratory virus disease, especially coronavirus.

Although with the low solubility and fast metabolism, its use in clinical practices might require a higher dose in humans with potential side effects such as DNA damage, lipid peroxidation, and cell death [62]. Hence, some areas to consider include the dose to use for its health benefits with no side effects. Different studies showing the antiviral activity of resveratrol *in vivo* at different doses and treatment days all observed decreased viral load.

For some decades, coronaviruses have shown to be a pathogen found in humans, though not much recognition was given until the outbreak of MERS-CoV (Middle East Respiratory Syndrome Coronavirus) and SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and also SARS-Cov-2 [75,76]. MERS-CoV and SARS-CoV have been traced to have originated from animal contact [76]. Phylogenetic analyses have shown that SARS-like coronaviruses found in bat was closely linked to SARS-Cov-2, and has about 79% similarity with SARS-CoV and 50% similarity with MERS-CoV [76].

Zhao *et al*. [77] revealed that in both *in vivo* and *in vitro* studies, resveratrol administration exhibited antiviral activities against different viral pathogens [77]. Resveratrol also significantly inhibited the *in vitro* replication of MERS-CoV by inhibiting the production of RNA and other pleiotropic effects [78]. Zhao *et al*. [79] showed inhibition of viral replication and death rate by resveratrol in ducklings infected with duck enteritis virus. Resveratrol was able to suppress the pseudorabies virus *in vitro* by inhibiting intracellular viral multiplication [80]. Different doses of resveratrol supplementation in piglets inoculated with pseudorabies virus for seven days before infection significantly reduced the viral loads compared to the untreated group and high survival rates [79]. Although resveratrol had low bioavailability, the use of nanoparticle formulations may improve stability and absorption [81,82]. Presently, no data have used resveratrol in the treatment of SARS-CoV-2; however, available studies showed that it might be an adjunctive antiviral agent to consider.

9. Cardioprotective Activity of Resveratrol

Cardioprotective activity is the mechanism of action that aids heart protection by reducing or preventing myocardial damage. Bohm *et al*. [83] revealed that resveratrol decreases the death rate related to coronary heart disease. Due to its antioxidant activities, resveratrol increases vasodilation, decreases aggregation of platelet, suppresses low-density lipoprotein oxidation, and promotes the activity of endothelial nitric oxide synthase, thereby suppressing atherosclerotic changes and ultimately enhancing the cardioprotective effect. Four weeks of resveratrol injection (1 mg/kg/day i.p.) in Sprague Dawley rats effectively suppressed the infarct size, which shows a potent cardioprotective effect. The echocardiographic analysis showed significantly improved left ventricle systolic and diastolic function. Expression of TGF-b1 mRNA and atrial natriuretic peptide level was analyzed with a quantitative PCR method, which was higher in the untreated groups than those treated with resveratrol [84]. Another possible mechanism for the cardioprotective activity in human cardiac cells could be as a result of the increase in the NF-kB activity [85]. In hypertensive rats, resveratrol protected both the cardiac and vascular tissues by decreasing ROS accumulation, thereby revealing its potential to increase its therapeutic approaches [86]. Also, some clinical trials have shown the cardioprotective activity of resveratrol [87].

In different animal models, doxorubicin-induced cardiotoxicity has been reported to be mitigated by the use of resveratrol [88-93]. Multiple mechanisms could be responsible for the protective effect of resveratrol especially ROS generation [94], inducing antioxidant enzymes such as SOD [90,91,95-97], catalase [90,95,97], NADPH quinine-oxidoreductase- 1 [95], and heme oxygenase-1.

Other mechanisms of cardiotoxicity protection include AMPK activation [98], inhibition of p70S6K-mediated autophagy [99], and activation of SIRT1 [96].

Resveratrol has shown high antiviral potential in both human and animal viral infections by inhibiting viral protein synthesis, viral related gene expressions, and inhibiting transcription and signaling pathways [6].

10. Conclusions

This review has explored the possibility of using chloroquine and hydroxychloroquine in the treatment of SARS-CoV-2, considering the present experiment using *in vitro* and *in vivo* clinical trials. We also explore resveratrol as an antiviral agent and a possible treatment option for SARS-CoV-2 infection or slows down its progress. However, some toxicity might be associated with these drugs (chloroquine and hydroxychloroquine). What we thought to be effective may later be more harmful. However, we suggest resveratrol due to its cardio-protective activities to mitigate the side effect of chloroquine and hydroxychloroquine. There is an urgent need for effective treatment against SARS-CoV-2 but the synergistic use of drugs with proven antiviral properties and could mitigate any potential side effects that could involve long term use could be explored.

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Conflicts of Interest

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