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Quinacrine as a potential treatment for COVID-19 virus infection

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Abstract. – A novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a current outbreak of infection termed Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). COVID-19 is currently a global pandemic that may cause close to half a billion deaths around the world. Until now, there is no effective treatment for COVID-19. Quinacrine (Qx) has been used since the 1930s as preventive antimalarial compound. It is a recognized small molecule inhibitor of RNA virus replication, with known anti-prion activity, and identified as a potent Ebola virus inhibitor both *in vitro* and *in vivo*. Recently, Qx has showed anti-SARS-CoV-2 activity. Herein, we review the potential mechanisms associated with quinacrine as an antiviral compound.

Key Words:
Quinacrine, SARS-CoV-2, COVID-19, Antiviral.

Introduction

Around the world, the scientific community is facing a pandemic provoked by a virus from the family Coronaviridae, order Nidovirales and denominated SARS-CoV-2 that is the causal agent of COVID-19 pandemic[1,2]. SARS-CoV-2 has a positive-sense single-stranded RNA transmitted mainly from human to human through respiratory droplets[3-5]. The envelope spike protein of the SARS-CoV-2 can attach the human angiotensin-converting enzyme II (ACE2) as an entry receptor. ACE2 is expressed in several human tissues including lungs, small intestine, kidneys, heart, thyroid, and adipose tissue[6].

The SARS-CoV-2 infection mainly exhibits flu-like symptoms such as fever, cough, and asthenia, similar to other coronaviruses[7,8]. It has been reported that high-risk individuals such as elderly subjects or those affected by multimorbidities such as hypertension, diabetes mellitus, and cardiovascular disorders, in which the virus produces acute respiratory failure and consequently it can reach to a high death rate[9]. The world faces its worst public health crisis in the modern era, and the disease continues to spread without any effective treatment. Consequently, there is an urgent necessity to find effective treatments to reduce its dissemination until successful prevention method is developed through vaccination. Currently, there is no existence of any effective treatment against COVID-19 and clinical management is only symptomatic[10].

Actually, the current pharmacological therapy for COVID-19 is focused on drugs with antiviral activity (ribavirin, lopinavir, remdesivir, plasma/immunoglobulin, chloroquine/hydroxychloroquine), immunomodulators (interferons and corticosteroids), and supplements (vitamin C, alpha lipoid acid)[11-14]. Herein, we proposed the research of quinacrine, an antimalarial drug with potential antiviral effects along with immunomodulatory properties.

Quinacrine Background

Quinacrine is an aminoacridine, discovered in the 1920s, that has been used for the treatment of malaria since 1931. It is worth mentioning that its use was empirical during the first years of World War II. The suppressive antimalarial activity of quinacrine (also known as atabrine or mepacrine) was examined in both *Plasmodium vivax* and *Plasmodium falciparum* infections induced by blood inoculation. Quinacrine was 200 times more active than quinine, thus, the oral dose of quinacrine was around one-third of that required of quinine[15]. Quinacrine was also

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effective to reduce around 97% of the tissue damage induced by amebic hepatitis[16]. Quinacrine inhibited the growth of *Histoplasma capsulatum in vitro* and contributed to decreasing the mortality rates of infected mice[17]. In 1937, quinacrine was also used to treat giardiasis, and it was found that doses similar to those given orally for malaria also eliminated giardiasis in children and adults[18]; similar satisfactory results were seen in Oriental sore[19].

Regarding its clinical use in patients, there are numerous studies about its pharmacological characteristics. It has been known that the main route of quinacrine administration is through oral intake, but it can be also administrated by intralesionally/paralesionally, intramuscularly, rectally, intravenously, transcervically, and interstitially. Quinacrine is rapidly absorbed from the gastrointestinal tract and also rapidly absorbed after intrapleural and intrauterine administration[20]. Plasma levels increase after 2-4 h after its intake and reaching a peak between 8-12 h. Quinacrine is widely distributed in tissue but it is liberated and eliminated slowly from the subject's body[21]. The administration of quinacrine produces some adverse reactions, most of which are minor or reversible (Table I). When quinacrine was administrated daily for long periods, it was shown that quinacrine was well tolerated, with few adverse effects (dermatitis, corneal edema and occasional anaemia for 1 in 20,000 samples)[22].

Nevertheless, quinacrine use for malaria, giardiasis, and tapeworm infections was supplanted by other drugs. In 1955, the introduction of hydroxychloroquine as antimalarial resulted in a decrease in quinacrine research. However, quinacrine was used for other purposes, such as a treatment of Lupus erythematosus and intrauterine sterilization[23-35]. In this context, it was showed that quinacrine is a safe method for the treatment of HIV-infected women[36]. Moreover, its high effectiveness against patients with nitroimidazole-refractory giardiasis was demonstrated[37].

Despite the favourable effects and adequate use of quinacrine profile with its pharmacokinetic properties and established record of safety[31], its clinical use has been abandoned. However, recent experimental studies show quinacrine as a potential therapy, not only as antimalarial and anthelmintic[38,39], but also as anticancer, anti-prion, and antiviral agent[40,41]. Recently, quinacrine has been tested in different trials of cancer (ClinicalTrials.gov identifiers: NCT01839955, NCT00417274, NCT01844076) and prion disease (NCT00183092, NCT00104663).

Mechanisms of Quinacrine for Antiviral Effects

Quinacrine is an acridine compound with antiviral properties. The first studies that demonstrated its antiviral effects were against equine encephalitis virus and louping-ill producing a

Table I. Adverse effects induced by quinacrine.

Quinacrine	Adverse effects	Reference
Children		
2 mg/kg three times daily × 5-7 days	28 % of study participants present bitter taste, nausea, and vomiting 4-5% of the study participants showed yellow/orange discolouration of the skin, sclerae, and had urine effects (started after a week of treatment) Nausea, vomiting, dizziness, and headache	Wolfe[23] Craft et al[24]
Adults		
Doses with adverse effects	Occasionally toxic psychosis (0.4% of incidence, reversible effect)	Farthing et al[25] Gardner et al[26]
100 mg three times daily, 5-7 days	After prolonged use: Yellow discolouration of the skin, sclerae and urine, chronic dermatoses, and aplastic anemia (0.003%)	Evans et al[27] Lindenmayer et al[28] Engel[29]
100 mg twice daily for 2 weeks	Exacerbate psoriasis and glucose-6-phosphate dehydrogenase-deficient individuals	Ward et al[30] Ehsanian et al[31]
200-1200 mg per day for 10 days	Cortical stimulatory effects, hyperirritability, insomnia, and nightmares	
Pregnant women		
Quinacrine ingestion during the first 4 weeks of gestation	Renal agenesis and hydrocephalus in an infant	Humphreys et al[32]

reduction in the amount of blood circulating virus during the early systemic phase of the infection. A protective effect was also observed when the virus was injected intracerebrally. Additionally, when 1-10 lethal doses (LD100) were used, a single dose of quinacrine reduced the mortality from one to two-thirds as compared with mice without treatment[42,43]. After these studies, the antiviral effects of quinacrine have been studied under several conditions (Table II) to determine the mechanisms by which quinacrine possesses antiviral properties. Divergent results explained by diverse factors, such as the severity of viral infection, site of the infection or the virus strain, have been reported[43,44].

Among the mechanisms by which this acridine compound possess antiviral properties are: quinacrine binds strongly to DNA with the association constant of 1.2×10^6 M^{-1} and stoichiometry of 1 quinacrine molecule/~ 4 nucleotides, being the 9-imino group of quinacrine involved in this intercalation binding[45]. Studies with polarized fluorescence showed that the quinacrine bound to flowing DNA, being the plane of the quinacrine ring nearer to the nucleotide bases than that of the helical axis of DNA[46]. Additionally, quinacrine restricts the conformational flexibility of the DNA and thus strengthening the ability of topoisomerase II to form a 'cleavable complex' in which DNA is covalently linked to the enzyme[47].

Spectroscopic and isothermal titration calorimetry studies showed that quinacrine binding is preferred to the HL-form of the RNA than to the A-form; while thermodynamic parameters showed that the binding of quinacrine to RNA reveals entropy-driven intercalation with no differentiation to A-form or HL-form of RNA[48]. Hence, quinacrine is a DNA and RNA strong intercalating substance preventing structural perturbation of DNA which renders it as a poor substrate for endonucleolytic cleavage interfering with the process of viral replication[49]. In this context, quinacrine and chloroquine, both antimalarial drugs inhibit the Tat-mediated long terminal repeat-drive gene expression necessary for replication of human immunodeficiency virus type 1 (HIV-1). It has been reported that quinacrine has a higher antiproliferative effect as compared to chloroquine[50]. Also, quinacrine binds to heparin and affects the interaction between heparin interacting peptide from Tat (which acts as a potent transactivator and it is crucial for viral replication) and heparin[51]. Moreover, it has been shown that quinacrine inhibits DNA polymerase of Hepatitis B virus[52], inducing an Interferon-like substance [44] and it is a strong inhibitor of somatic mutations[53,54].

A recent report shows that quinacrine inhibits the initiation of translation of encephalomyocarditis virus (EMCV), hepatitis C virus, and poliovirus internal ribosome entry sites (IRESs) in a cell-free translation assay and it has also been demonstrated that quinacrine binds the viral IRES by a competition dialysis system test. Additional experiments showed that production of EMCV and poliovirus capsid proteins, as well as replication of virus RNAs, was suppressed by quinacrine in HeLa cells infected reducing virus generation without disrupting the internal cellular IRES[55]. The same effects on RNA intercalation, inhibition of RNA transcription, and protein synthesis without disrupting internal cellular IRES was observed with Enterovirus 71[56]. Additionally, it has been shown that quinacrine inhibits RNA accumulation of RNA tomato bushy stunt virus (TBSV) in plants and protoplasts[57]. *In vitro* studies have shown that quinacrine inhibits the binding of protein p33, which is essential as replication co-factor of the viral RNA template[58]; quinacrine reduces the minus-strand synthesis by the tombusvirus replicase. Additionally, the translation of TBSV genomic RNA was also inhibited by quinacrine[59].

Similarly, it has been reported that quinacrine inhibits phospholipase A2 (PLA2) without affecting phospholipase C[60,61] and reduces the cytotoxicity of gp120 protein of human immunodeficiency virus due to inhibition of phospholipase A2[62]. The inhibition of phospholipase by quinacrine also leads to a drop in the amount of choline liberated into the medium by poliovirus-infected cells[63]. Quinacrine inhibits the cytolytic activity of TNF-α through inhibition of phospholipase A2 activity[64].

Quinacrine is a lysosomotropic agent, its dual protonation at low pH induces cellular trapping that increases the endosomal pH. This property of quinacrine seems related to its inhibition of the acidification organelles of as lysosome, endosome, and secretory granules of exocrine cells, necessary for degradation of cell debris, signalling, and cell homoeostasis[65]. In this context, it has been proposed that quinacrine could interfere with the cellular mechanisms involved in the process of HIV infection[66]. Additionally, it was demonstrated that quinacrine reduced dengue virus (DENV2) titers and viral RNA copy numbers in infected cells. In the same study,

Table II. Quinacrine documented use as a treatment of experimental viral models.

	Model	Doses/ concentration quinacrine	Effects	Toxic effects induced by quinacrine	Reference
Equine encephalomyelitis	Mice	Single-dose 10 mg/18 g	Increased the survival of fatal cases and reduced the mortality by more than 72%.	Not reported	Hurst et al[42]
Louping-ill	Mice	Single-dose 10 mg/18 g	Increased the survival of fatal cases and reduced the mortality	Not reported	Hurst et al[42]
Western equine encephalomyelitis	Mice	Single-dose (10 mg/20 g) 24 h before virus lethal challenge	Increased the survival of fatal cases and reduced the mortality by around 91% as compared to the group of mice infected without treatment.	Not reported	Hurst et al[43]
St. Louis encephalitis	Mice	Single-dose (10 mg/20 g) 24 h before virus lethal challenge	Reduced mortality by 40%. Decreased virus titer.	Not reported	Hurst et al[43]
Rabies-virus-fixe	Mice	Single-dose (10 mg/20 g) 24 h before virus lethal challenge	No changes were found as compared to animals infected without treatment	Not reported	Hurst et al[43]
Rift Valley fever	Mice	Single-dose (10 mg/20 g) 24 h before virus lethal challenge	Increased survival periods of fatal cases. Decreased virus titer	Not reported	Hurst et al[43]
Neurotropic influenza – W.S. strain	Mice	Single-dose (10 mg/20 g) 24 h before virus lethal challenge	Increased the survival period and a reduction of around 50% in the deaths was reported as compared to untreated infected mice	Not reported	Hurst et al[43]
Lymphocytic choriomeningitis	Mice	Single-dose (10 mg/20 g) 24 h before virus lethal challenge	Increased the survival period of fatal cases and decreased the number of deaths. Decreased virus titer	Not reported	Hurst et al[43]
Herpes febrilis	Mice	Single-dose (10 mg/20 g) 24 h before virus lethal challenge	Increased the survival period of fatal cases with a decrement in the mortality.	Not reported	Hurst et al[43]
Herpes A	Mice	Single-dose (10 mg/20 g) 24 h before virus lethal challenge	Increased the survival period of fatal cases with a decrement in the mortality.	Not reported	Hurst et al[43]
Herpes B	Mice	Single-dose (10 mg/20 g) 24 h before virus lethal challenge	Increased the survival period of fatal cases with a decrement in the mortality	Not reported	Hurst et al[43]
Vaccinia virus	Mice	200 mg/kg, 22 h before virus infection	The decreased quantity of plaque-forming units as compared to a case with no treatment considered on mice	Not evaluated	Glaz et al[44]
Herpes simplex Virus 1	Ganglia culture	1×10^{-4}M	Inhibited the viral reactivation in the explanted ganglia, no virus titer was found	No cytotoxic was observed effect for the used concentration.	Kurane et al[72]
Hepatitis B virus	Preparation of hepatitis B antigen	100-800 µg/ml	Inhibited hepatitis B DNA polymerase (IC_{50} 334 µg/ml).	Not evaluated	Hirschman et al[52]
gp120 of HIV-1	Rat primary Neuronal Cell culture	Pretreatment (30 min before infection) 3-50 µM	Decreased gp120 cytotoxicity. Increased the percentage of viable cells (3 µM of Qx increased 28%)	Not evaluated	Ushijima et al[62]
HIV-1	Transfected cells	2-10 µM for 12 h	Inhibited Tat-induced transactivation and showed antiproliferative effects	Not evaluated	Jiang et al[50]

Continued

Table II *(Continued)*. Quinacrine documented use as a treatment of experimental viral models.

	Model	Doses/ concentration quinacrine	Effects	Toxic effects induced by quinacrine	Reference
Tomato bushy stunt virus (TBSV)	Nicotiana benthamiana protoplasts	5-20 μM	Inhibited TBSV accumulation around 50% when it was. applied before electroporation	Not evaluated	Sasvari et al[59]
	Nicotiana benthamiana leaves	1600 μM (*via* infiltration)	Inhibited TBSV RNA accumulation by 99%.		
	In vitro replicase assembly assay	20 μM	Inhibited TBSV replication (90-90%). Inhibited minus-strand synthesis by the tombusvirus replicase Inhibited the binding of p33 replication protein to the viral (+)RNA.		
Encephalomyocarditis virus (EMCV)	HeLa cells infected with EMCV	0-20 μM	Suppressed production of viral capsid proteins, replication of viral RNAs, and virus titer.	Not evaluated	Gasparian[55]
	Cell-free s ystem	25 μM	Inhibited 80% of translation from the EMCV Internal ribosome entry sites (IRESs).		
Poliovirus	HeLa cells infected with poliovirus	0-20 μM	Inhibited the synthesis of viral capsid proteins, production of viral RNAs, and virus replication in a dose-dependent manner.		
	Cell-free system	0-25 μM	Inhibited around 50-60% of translation from poliovirus IRES.	Not evaluated	Panavas et al[58]
Enterovirus 71 (EV71)	Rhabdomyosarcoma cells	1-20 μM	Inhibited viral RNA replication, viral capsid protein expression, and virus production. Protected cells from EV71.	Not evaluated	Wang et al[56]
Coxsackieviruses (CoxA10, CoxA1 and CoxB5)	Rhabdomyosarcoma cells	1-25 μM	Inhibited viral replication. Suppressed viral titer.	Not evaluated	Wang et al[56]
Echovirus (Echo25)	Rhabdomyosarcoma cells	1-25 μM	Inhibited viral replication (suppressed viral titer)	Not evaluated	Wang et al[56]
White spot syndrome virus	Pacific white shrimp Litopenaeus vannamei	5 μg/g	Reduced the mortality rate and viral copy number.	No mortality was found with quinacrine treatment.	Kang et al[73]
	Sf9 cells transfected with the bicistronic plasmid containing the icp35 IRES element	25-30 μM	Suppressed icp53 IRES activity. Increased cell viability.		

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the authors demonstrated that quinacrine inhibits autophagy increasing pH and, as consequence, inhibits infection by dengue virus[67]. Also, quinacrine inhibits cathepsin B which is involved in LC3-II proteolysis. Quinacrine has recently been proposed as an active drug against Ebola virus (EBOV); decreasing the EBOV infection *in vitro* and *in vivo* protecting 70% of mice from a lethal challenge with mouse-adapted EBOV suggesting that this protective effect was induced by quinacrine raising the pH of acidic cytoplasmic organelles inhibiting the enzymatic activity of viral

Table II *(Continued)*. Quinacrine documented use as a treatment of experimental viral models.

	Model	Doses/ concentration quinacrine	Effects	Toxic effects induced by quinacrine	Reference
Ebola virus (EBOV)	HeLa cells treated with infection mix containing Ebola-GFP virus	0.12-250 μM	Decreased Ebola infection (EC_{50} 350 nM).	CC_{50} 6.2 μM	Ekins et al[74]
	EBOV-infected HeLa cells	EC_{50} 0.5-0.98 μM	Decreased EBOV activity.	CC_{50} ~7.94 μM	Anantpadma et al[69]
	Mouse-adapted EBOV	25 mg/kg	Increased survival rate by 70%.	50 mg/kg of quinacrine decreases by 50% of the effect observed with 25 mg/kg in survival.	Lane et al[68]
Dengue virus	HEK293 cells noculated with DENV-2	5 nM and 10 μM	Inhibited 94% of infection, CI_{50} 0.53 ± 0.04 μM.		Shum et al[75]
	BHK-21 cell line stably expressing DENV2 RNA	0.78-200 μM	Reduced DENV2 titers (CI50 7.09 ± 1.67 μM) and DENV2 viral RNA copy numbers.	CC_{50} 44.48 ± 16.45 μM	Balasubramanian et al[67]
Zika virus	Vero cells transfected with Zika virus (MR766)	0-200 μM	Inhibited Zika virus infectivity (EC50 2.27 ± 0.14 μM) Inhibited Zika replication.	CC_{50} 18.59 ± 3.15 μM	Balasubramanian et al[67]
SARS-CoV-2	Lung and Colonic Organoids Vero cells		Inhibited viral replication and virus entry with EC_{50} = 0.84-3.01 μM through blocking ACE2 receptor.	CC50 6.2-22 μM	Han et al[71] Ianevski et al[76]

cell entry[68-70]. Recently, it has been described that Qx inhibited SARS-CoV-2 viral replication and viral entry by the Qx binding to angiotensin-converting enzyme 2 (ACE2) receptor[71].

Mechanisms Associated with Quinacrine Immune Modulator Effects

Since the 1950s, quinacrine has been used as an immunomodulator in asthma[72-78]. Afterwards, it was demonstrated that quinacrine had anti-aggregate activity by reduction of platelet-activating factor[79]. However, the most documented characteristic of quinacrine as an anti-inflammatory factor is through PLA2 inhibition[80]. Its anti-asthmatic activity was due to improved clinical features, as well as Th1/Th2 unbalanced response, simultaneously decreasing PLA2 activity and cysteinyl leukotrienes levels[81]. More recently, quinacrine has also been used as an immunomodulator in dermatomyositis and cutaneous lupus erythematosus, due to its ability to inhibit the secretion of proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α) from peripheral blood mononuclear cells (PBMCs)[82,83]. Coincidentally, TNF-α is a relevant cytokine participating in the cytokine storm that some COVID-19 patients with clinical complications develop.

Quinacrine has shown inhibition of intracellular TLRs 7 and 9, two ligands involved in the innate immune response by recognition of single-chain RNA and CpG motifs, inhibiting the secretion of proinflammatory cytokines and antigen presentation by peripheral blood mononuclear cells (PBMCs)[84,85]. Recently, Zhou et al[86] elaborated a network-based drug for therapeutic trials against novel coronavirus 2019-nCoV/SARS-CoV-2, in that list, quinacrine appears at the top of 16 network-predicted repurposable drugs.

Quinacrine as a Potential Anti-SARS-CoV-2 Agent

Quinacrine has several documented possible targets for SARS-CoV-2 replication inhibition. As the authors have mentioned before, SARS-CoV-2 is a positive single-stranded RNA virus with nucleocapsid. Therefore, quinacrine could intercalate within the SARS-CoV-2 RNA, inhibiting both, RNA transcription and protein synthesis, without disrupting the internal cellular IRES. Additionally, after SARS-CoV-2 cell entry via endosomes quinacrine, as a lysosomotropic agent, might increase the pH in the endosomes and lysosomes, thus, inhibiting lysosomal proteases and the fusion of autophagosome and lysosome preventing the release of viral material into the endosomes and autophagolysosomes (Figure 1).

In addition to these antiviral properties, quinacrine has several characteristics that suggest immune modulator effects. Quinacrine acts as anti-inflammatory through PLA2 inhibition inhibiting the formation of arachidonic acid, COX activation and cysteinyl leukotrienes formation. Moreover, quinacrine inhibits intracellular TLRs 7 and 9, ligands of single-chain RNA involved in the activation of the innate immune response against SARS-CoV-2 infection, which decrease the secretion of proinflammatory cytokines by peripheral blood mononuclear cells (PBMCs) without affecting the production of Type I interferons (IFN-α and IFN-β). These properties would allow quinacrine to limit the cytokine storm-generated in some COVID-19 patients without affecting the antiviral immune response (Figure 2).

Conclusions

In summary, the vast information about the medical uses of quinacrine by millions of patients and its experimental efficacy inhibiting virus replication supports the idea that quinacrine may be useful as adjuvant antiviral compound against SARS-COV-2 virus. Additionally, its effects on the innate immune response and on reducing the cytokine storm make quinacrine as a reliable candidate for the clinical test to repurposing it for therapy of SARS-COV-2

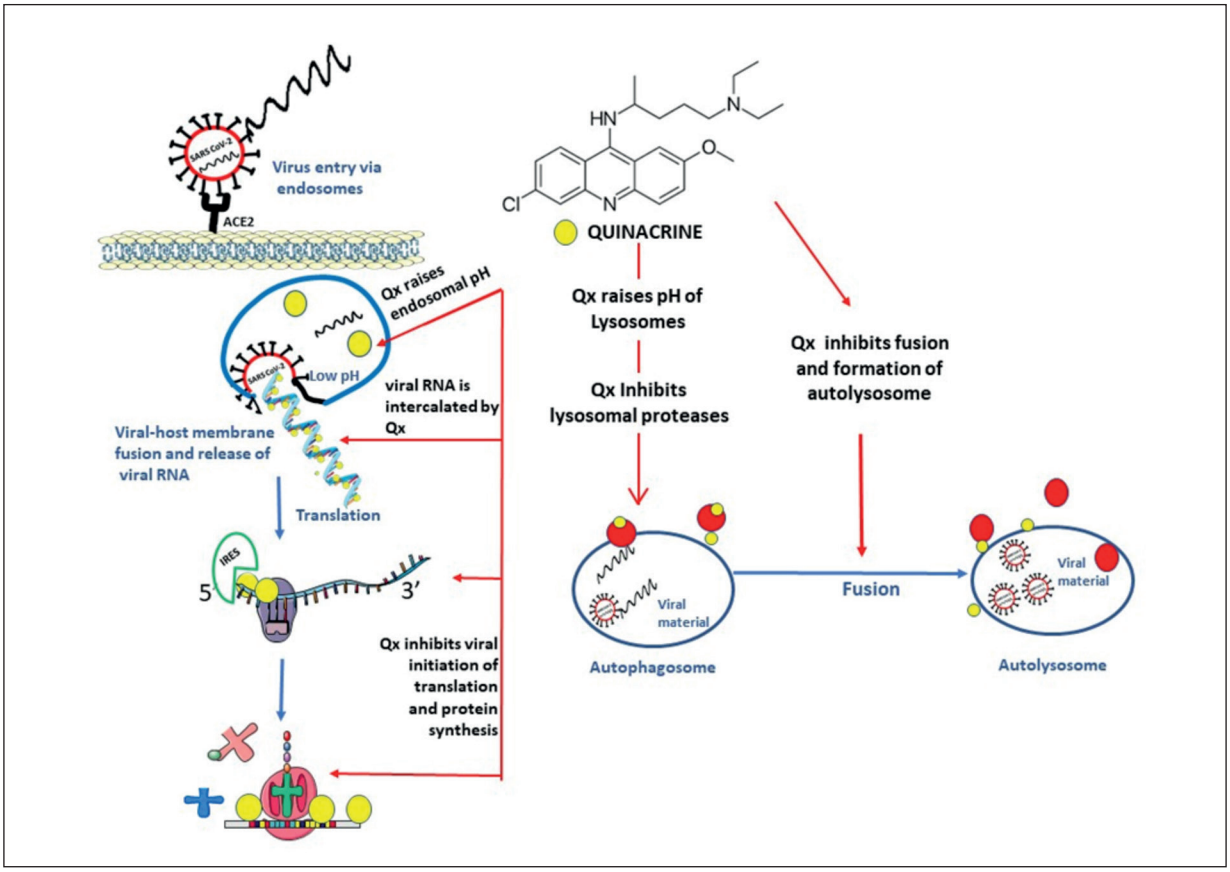

Figure 1. Potential anti-SARS-CoV-2 mechanisms of quinacrine.

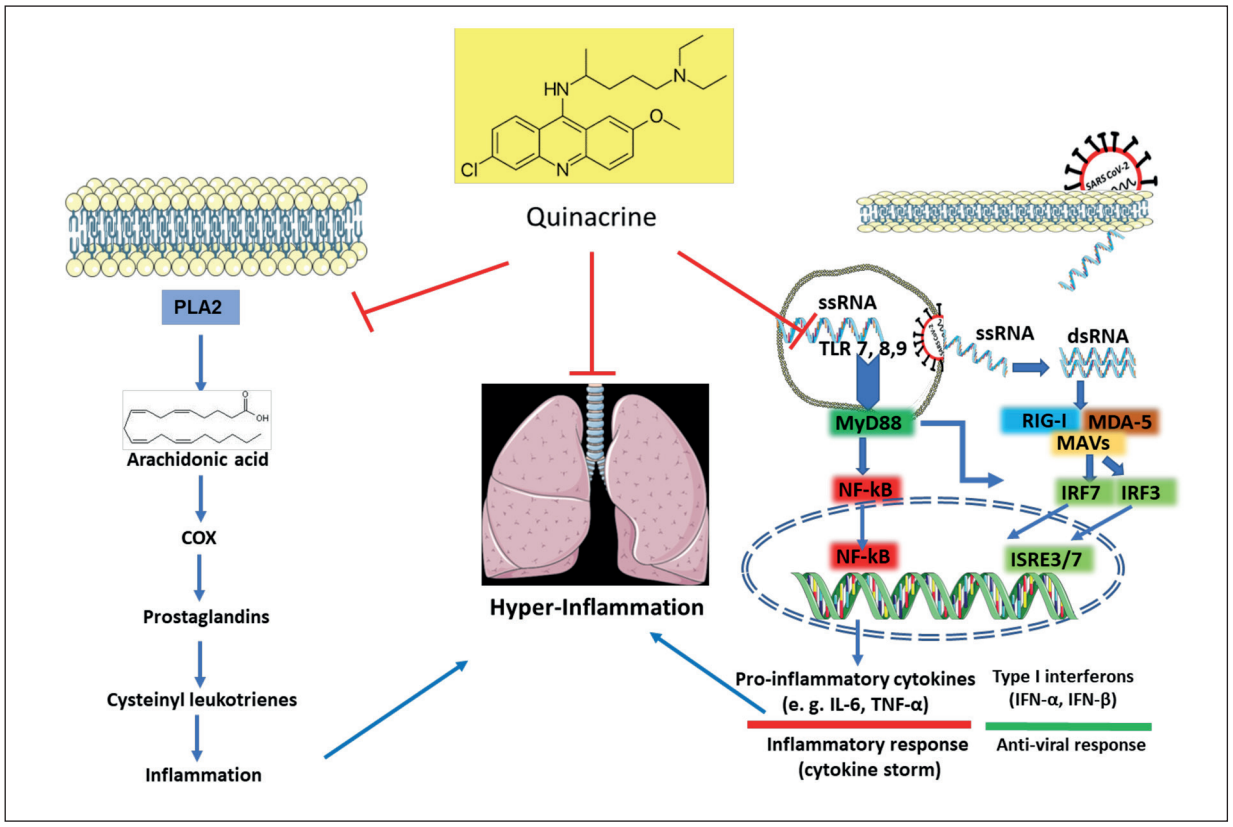

Figure 2. Immune modulator effects of quinacrine in COVID-19.

virus disease, alongside to the current drugs being evaluated under the headlines of compassionate use. Actually, several groups are currently working to evaluate the anti-SARS-CoV-2 potential of quinacrine therapy as a possibility to enter clinical trials for new indications.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

Conceptualization: B.P.; Investigation: VPC, RHP and J.S.; writing—review and editing, B.P., V.P.C., R.H.P. and J.S. All authors have read and agreed to the published version of the manuscript..

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