*Communication*

# Evidence That Quinine Exhibits Antiviral Activity against SARS-CoV-2 Infection *In Vitro*

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**Abstract:** Since there is no vaccine or regulatory approved therapy available for treatment of SARS-CoV-2 infection, the medical need to prevent the transition of a mild into the severe COVID-19 stage of infection is of outmost importance. Among several drug candidates, Chloroquine (CQN) and Hydroxy-Chloroquine (H-CQN) have been tested most intensively. However, the therapeutic effect of H-CQN and CQN has been discussed controversially in the light of severe side effects. Originally, H-CQN descended from the natural substance Quinine, a medicinal product used since the Middle Ages and is now regulatory approved for various indications. We hypothesized that Quinine also exerts anti-SARS-CoV-2 activity. First, virus production in Vero B4 cells was analyzed by Western blot, showing that Quinine exerts antiviral activity against SARS-CoV-2 that at 10 µM was even stronger than that of H-CQN or CQN. Second, fluorescence end-point and time lapse analysis of SARS-CoV-2-mNeonGreen-infected Caco-2 cells could confirm a similar antiviral effect of Quinine in a human-derived cell line. Thereby, our *in vitro* studies revealed, that the antiviral effect appears to be specific, since in Vero cells Quinine impacted cell viability at approximately 50-fold higher concentration, while the therapeutic window of H-CQN and CQN was approximately 10-fold lower. In Caco-2 cells no toxic effect was observed while complete block of infection occurred between 50 and 100 µM at high MOIs. In conclusion, our data indicate that Quinine would have the potential of a well tolerable and widely used treatment option for SARS-CoV-2 infections, with a predictable and significantly better toxicological profile when compared to H-CQN or CQN.

**Keywords:** SARS-CoV-2; Quinine; Hydroxy-Chloroquine; Chloroquine; COVID-19; antiviral

## 1. Introduction

In the last two decades, three coronaviruses, SARS-CoV, MERS, and very recently, SARS-CoV-2 emerged from the animal kingdom, causing in each case life-threatening diseases, particularly as non-immunocompetent populations were encountered. Infection with SARS-CoV-2 can cause the multi-organ disease COVID-19 (Corona virus disease 2019) resulting, among other pathologies, in the acute respiratory distress syndrome (ARDS), a clinical condition of acute lung injury with severe hypoxemia [1]. 80% of all SARS-CoV-2 infected people remain asymptomatic or develop only mild symptoms, while others require hospitalization [2]. Until now, there is no vaccine or specific antiviral therapy available. There is anecdotic evidence that plasma of convalescent patients can support recovery from COVID-19 [3]. However, even if proven effective, the supply of plasma would be

limited. For direct antiviral therapy, some repurposed drugs are in clinical development: Remdesivir, a nucleotide analog originally developed to cure Ebola infection; Favipiravir, an inhibitor of the viral RNA-dependent RNA polymerase showing activity against many RNA viruses; Ritonavir and Lopinavir, both HIV-1 protease inhibitors; as well as the Hydroxy-Chloroquine (H-CQN) and its related Chloroquine (CQN) (Fig. 1 C), drugs which are commonly used for malaria treatment and for autoimmune diseases, e.g. rheumatoid arthritis and systemic lupus erythematosus [4-7]. Originally, H-CQN was first shown to interfere with SARS-CoV-2 replication *in vitro* [8]. Furthermore, of all drug-candidates H-CQN and CQN have been tested most intensively in clinical studies. China has recommended H-CQN for treatment of hospitalized COVID-19 patients [9]. In the US, H-CQN and CQN are being fast-tracked through clinical trials in order to determine their efficacy in the treatment of COVID-19, although this recommendation is retracted nowadays [9]. Until now, at least seven clinical studies have shown that H-CQN and/or CQN are effective against SARS-CoV-2, whereas seven studies have shown no efficacy [3, 10-22]. Considering the fact that H-CQN inhibits virus entry, it should be administered early after infection, before the transition to severe COVID-19. H-CQN and CQN were shown to increase the pH of acidic organelles, such as endosomes, thereby interfering with the receptor-mediated endocytosis of the virus [23, 24]. Consistent with entry inhibition, a very recent clinical trial report concludes that treatment with H-CQN should start as early as possible after hospitalization [3]. H-CQN and CQN were also shown to enter lymphocytes and macrophages leading to a reduction in inflammatory response which might suppress the cytokine storm associated with the COVID-19 progression [23]. This is in concert with a recent study showing that low doses of H-CQN have a therapeutic effect even in the late COVID-19 stage in terms of attenuation of the inflammatory cytokine storm [3]. However, the therapeutic effect of H-CQN and CQN has been controversially discussed in the light of severe side effects associated with these drugs, e.g. gastrointestinal problems, visual and hemogram disorders, cramps, cardiac arrhythmias (prolonged QT syndrome) and retinopathy [25-27]. Therefore, the usage of H-CQN or CQN requires physician's monitoring and cannot be administered "over the counter".

If SARS-CoV-2 would cause a pathogenic profile similar to typical seasonal coronaviruses without transition into the severe COVID-19 stage, the world would be enfranchised from one of its most serious current problems. Thus, there is a tremendous medical need to prevent the transition of a mild SARS-CoV-2 infection into a severe COVID-19 stage by having access to a safe, relatively cheap and easily distributable drug. Thereby, a less toxic variant of H-CQN or CQN would be such a promising treatment option. However, the optimization of H-CQN and CQN by medical chemistry followed by preclinical and clinical development of such an improved drug would effort time, high costs, and would be no option to interfere with the current pandemic.

Looking at the history, H-CQN and CQN are derivatives from their natural predecessor Quinine, an extract of the bark of the Chinchona tree (native to the Andes of South America), that was used to treat feverish infections, particularly malaria, for hundreds of years almost worldwide [9, 28]. Quinine and Quinidine, both content of the Chinchona bark, are alkaloids and stereoisomers of each other [9]. The first records for medical use of Quinine date back to 1630, where in Peru the countess of Chinchon developed malaria and was successfully treated with an extract of the bark of the "fever tree", which was later termed Chinchona bark [29]. First isolated in 1820 and chemically synthesized in 1944 it was the only antimalarial drug available [29]. In the 19$^{th}$ century, British citizens and soldiers used tons of the Chinchona bark to protect themselves from malaria and thus permitted a stable British population in tropical colonies. Based on this natural product, H-CQN was synthesized in 1946 and mainly used for the treatment of malaria. Nevertheless and even until now, Quinine is used for treatment of severe and H-CQN-resistant cases of Malaria tropica [30]. As a medicinal product Quinine has considerably fewer side effects than H-CQN. It is also approved for the treatment of calf cramps (brand name: "Limptar N", Cassella Med GmbH). In addition, Quinine is commonly used as an aromatic agent. For instance, it is added to bitter lemon and tonic water. Quinine has been commercialized since the 19$^{th}$ century in beverages, known as "Indian Quinine Tonic". The latter was the standard beverage for the pioneers in malaria invested tropical areas. Particularly British soldiers mixed tonic water with lime and gin. Winston Churchill said: *"The gin and tonic has saved more*

*Englishmen´s lives, and minds, than all the doctors in the Empire"* [31]. Quinine can be added up to 100 mg/kg for food or up to 85 mg/l to beverages and up to 250 mg/l to alcoholic beverages [32]. Quinine has antimicrobial activities useful for treatment of bacteria and viruses. For instance, it has been shown *in vitro* that Quinine has antiviral activity against Dengue, Herpes simplex, and Influenza A viruses [33-35].

Given the fact that H-CQN and CQN are active against SARS-CoV-2 it was intriguing to hypothesize that also the original natural substance Quinine might exert antiviral activity against SARS-CoV-2. By asking this question, we tested Quinine in two versions: (i) Quinine-sulfate extracted from a tablet (Limptar N, Cassella Med GmbH), termed "*Q-Limptar*", and (ii) Quinine-sulfate as solid material directly obtained from a supplier (Sigma), termed "*Q-Sigma*". Our data suggests that Quinine exerts antiviral activity against SARS-CoV-2 in a manner superior to the antiviral effect of H-CQN and CQN. If our data would hold up *in vivo*, it would be legitimate to conclude that the usage of Quinine for the treatment of SARS-CoV-2 infections would display a tremendous improved toxicity profile compared to H-CQN and CQN.

## 2. Materials and Methods

### 2.1 Cell Culture and Infection

Vero B4 cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% (v/v) inactivated fetal calf serum (FCS), 2 mM l-glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin. Confluent monolayers of Vero B4 cells were infected in FCS free DMEM with a 100-fold dilution of the field isolate SARS-CoV-2$_{PR-1}$ for 1h and afterwards treated with interventions. 72 hours post infection, cells were lysed in radio immunoprecipitation assay (RIPA) buffer (150 mM NaCl, 50 mM Tris-HCl pH 8.0, 1% NP-40, 0.5% Na-deoxycholate, 0.1% sodium dodecyl sulfate (SDS), 10 mM ethylenediaminetetraacetic acid (EDTA)) containing protease inhibitor cocktail Complete (Roche, Basel, Switzerland), 5 mM N-ethylmaleimide (NEM), and 1 mM phenylmethylsulfonylfluoride (PMSF) and further used for Western Blot analysis.

Caco-2 (Human Colorectal adenocarcinoma) cells were cultured at 37 °C with 5% $CO_2$ in DMEM containing 10% FCS, with 2 mM l-glutamine, 100 µg/ml penicillin-streptomycin and 1% NEAA. For infection experiments, 1 ×$10^4$ Caco-2 cells/well were seeded in 96-well plates the day before infection in media containing 5% FCS. Cells were infected with the SARS-CoV-2 strain icSARS-CoV-2-mNG at a MOI=3 or mock-infected during 1h at 37°C. 1 hour post infection (hpi) the inoculum was removed and the cells were treated with the inhibitors in concentrations from 0-100 µM during 48 h at 37°C. A time-course of the infection was recorded using Cytation3 (Biotek). Images of bright field and mNeonGreen [500,542] were taken every hour during 48 h at 4-fold magnification. After treatment, the cells were fixed with 2% PFA and stained with Hoechst (1 µg/mL final concentration). For quantification of infection rates images were taken with the Cytation3 (Biotek) and Hoechst+ and mNeonGreen+ cells were automatically counted by the Gen5 Software (Biotek).

### 2.2 Isolation of SARS-CoV-2$_{PR-1}$

From a 61 years old patient nasal and pharyngeal swab was taken 6 days after presumed date of infection and 2 days after start of mild symptoms of COVID-19. This first swab was positive by real-time-PCR (according to the Charité protocol) with Ct value of 15, further follow-up swab after 10 days was still positive with Ct value of 31, further follow-up swabs 18, 19 and 35 days after the first swab remained negative.

2.3 Viruses

The recombinant SARS-CoV-2 expressing mNeonGreen (icSARS-CoV-2-mNG) [36] was obtained from the World Reference Center for Emerging Viruses and Arboviruses (WRCEVA) at the UTMB (University of Texas Medical Branch). To generate icSARS-CoV-2-mNG stocks, Caco-2 cells were infected, the supernatant was harvested 48 hpi, centrifuged and stored at -80°C. For MOI determination, a titration using serial dilutions of the virus stock was conducted. The number of infectious virus particles per ml was calculated as the (MOI × cell number)/(infection volume), where MOI = −ln(1 − infection rate).

The virus strain SARS-CoV-$2_{PR-1}$ was amplified in Vero B4 cells. Viral titers were determined by an endpoint titration assay. For the generation of new virus stock, virus containing cell culture supernatant was harvested 72 hpi and passed through a 0.45 µm pore-size filter. Virus stocks were stored at −80 °C until further usage. For Western Blot analysis, Vero B4 cells were infected with SARS-CoV-$2_{PR-1}$ (multiplicity of infection (MOI): $10^{-3}$) for 1 h and further treated with interventions. 72 hpi, virus-containing cell culture supernatants were harvested and released virions were purified through 20% (*w*/*v*) sucrose cushion (20,000× *g*, 4 °C, 90 min).

For MOI determination of SARS-CoV-$2_{PR-1}$ virus stocks Vero B4 cells were infected with serial dilutions of the virus stock over 72 h. Afterwards cells were fixed (4% PFA), permeabilized (0.5 % Triton/PBS), blocked (1% BSA/PBS-T) and finally stained with a SARS-CoV-2 NP antibody (Biozol). Endpoint of virus infection was analyzed via fluorescence microscopy and viral titer was calculated by the method of Reed and Muench [37].

2.4 Inhibitors

*Q-Sigma* as well as CQN were obtained from Sigma-Aldrich (St. Louis, Missouri, US) and dissolved in DMSO. 200 mg *Q-Limptar* (brand name: "Limptar N", Cassella Med GmbH, Germany), was extracted from a tablet, pulverized and dissolved in DMSO resulting in a stock solution of 12.5 µM. 200 mg H-CQN was acquired as a tablet (Eberth, Ursensollen, Germany), pulverized and dissolved in DMSO resulting in a stock solution of 20 mM. All interventions were used at the concentrations indicated in the different experiments.

2.5 SDS-PAGE and Western Blotting

Protein samples were separated by SDS-PAGE, transferred onto nitrocellulose membranes, blocked with 3% bovine serum albumin and incubated with the appropriate primary antibody (Ab). Viral proteins were detected by antibodies derived from convalescent SARS-CoV-2 patient sera. The anti-β-actin antibody was purchased from Sigma-Aldrich (St. Louis, MO, USA). The anti-human and anti-rabbit secondary antibodies coupled to horseradish peroxidase (HRP) were obtained from Dianova (Hamburg, Germany).

2.6 Determination of the amount of viral RNA copies from released viruses by qRT-PCR

Virus was quantified by real-time PCR AgPath-ID One-Step RT-PCR Kit from Ambion (Cat: 4387424) allowing reverse transcription, cDNA synthesis and PCR amplification in a single step. Samples were analyzed by 7500 software v2.3 (applied Bioscience). PCR primers were used according to [38]: RdRp_fwd: 5′-GTG-ARA-TGG-TCA-TGT-GTG-GCG-G-3′ and RdRp_rev 5′-CAR-ATG-TTA-AAS-ACA-CTA-TTA-GCA-TA-C-3′. Probe was 5′--CAG-GTG-GAA-/ZEN/CCT-CAT-CAG-GAG-ATG-C -

3′ (Label: FAM/IBFQ Iowa Black FQ). As positive control a specific target for E and RdRp gen of SARS-CoV2 was used and made by Integrated DNA Technologies. Control: 5′-TAA-TAC-GAC-TCA-CTA-TAG-GGT-ATT-GAG-TGA-AAT-GGT-CAT-GTG-TGG-CGG-TTC-ACT-ATA-TGT-TAA-ACC-AGG-TGG-AAC-CTC-ATC-AGG-AGA-TGC-CAC-AAC-TGC-TTA-TGC-TAA-TAG-TGT-TTT-TAA-CAT-TTG-GAA-GAG-ACA-GGT-ACG-TTA-ATA-GTT-AAT-AGC-GTA-CTT-CTT-TTT-CTT-GCT-TTC-GTG-GTA-TTC-TTG-CTA-GTT-ACA-CTA-GCC-ATC-CTT-ACT-GCG-CTT-CGA-TTG-TGT-GCG-TAC-TGC-TGC-AAT-ATT-GTT-3′

2.7 Assessment of Cell Viability

Viability of infected and treated cells was assessed by the water-soluble tetrazolium salt (WST)-1 assay (Roche) according to the manufacturer's instructions.

2.8 Software and statistics

We used Microsoft Word and Excel. GraphPad Prism 8.0 was used for statistical analyses and to generate graphs. Figures were generated with CorelDrawX7. Other software used included Gen5 v.3.04.

**3. Results**

In order to analyze if Quinine displays antiviral activity against SARS-CoV-2, first, Vero B4 cells were infected with SARS-CoV-2$_{PR-1}$ and treated with Quinine, either as *Q-Limptar* or as *Q-Sigma*, and, as a positive control, with H-CQN or CQN. 3 days post infection (dpi) cell culture supernatants were harvested and virus production was analyzed by Western blot (Fig.1). Intriguingly, treatment with Quinine leads to a strong reduction of SARS-CoV-2 replication. At 10 µM the production of progeny virions was almost completely blocked (Fig. 1 A, B). The level of antiviral activity was independent of whether Quinine was added as *Q-Limptar* (Fig.1 A) or *Q-Sigma* (Fig. 1 B). Most astonishingly, Quinine displays an even higher efficacy in the inhibition of SARS-CoV-2 replication than H-CQN or CQN: at 10 µM Quinine the replication was reduced by up to 90%, whereas 10 µM H-CQN leads to a reduction of ~50% (Fig 1 B).

Thus, these cumulative data implicate that Quinine exhibit strong antiviral activity against SARS-CoV-2, which is even stronger than the described antiviral activities of H-CQN and CQN [8].

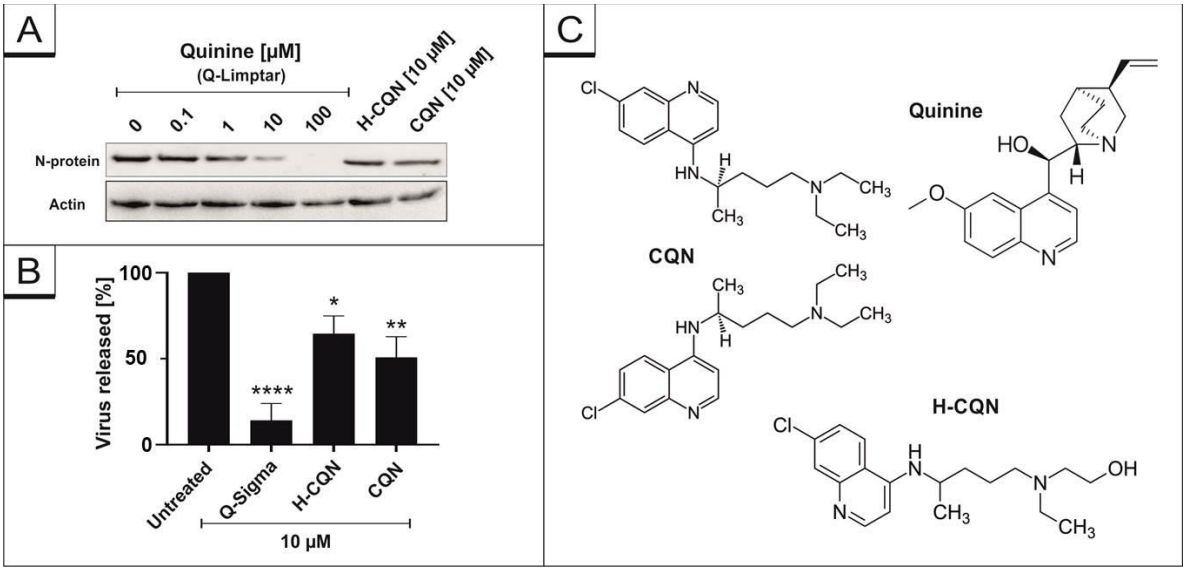


**Figure 1.** Influence of Quinine, H-CQN and CQN on the replication of SARS-CoV-2 in Vero B4 cells. (A) Western blot analysis of virus fractions (N-protein=Nucleoprotein). The cell fractions were stained

with ß-actin antibody. Quinine-sulfate was used as *Q-Limptar* (A) or *Q-Sigma* (B). Cell culture supernatants were harvested 3 dpi. The virions were purified and analyzed by Western blot using a SARS-CoV-2 convalescent serum. (B) Densitometric analysis of Western blot analysis was performed using AIDA®. Analysis of five independent experiments ± standard deviation (SD) (Q-Sigma $p<0.001$), three independent experiments ±SD (H-CQN $p=0.0270$) or four independent experiments ±SD (CQN $p=0.0039$). (C) Molecular structures of Quinine, H-CQN and CQN.

To control for potential unspecific effects of drug treatment on cell viability, water-soluble tetrazolium salt (WST)-1 assays were performed in uninfected Vero B4 cells showing that treatment at concentrations which effectively suppressed SARS-CoV-2 replication had no impact on cell viability (Fig. 2 A+B). In Vero cells the $TD_{50}$ was ~300 µM for Q-Limptar (Fig. 2 A) and ~100 µM for Q-Sigma (Fig. 2 B), which is again better than that of H-CQN and CQN (~50 µM) (Fig. 2 C+D).

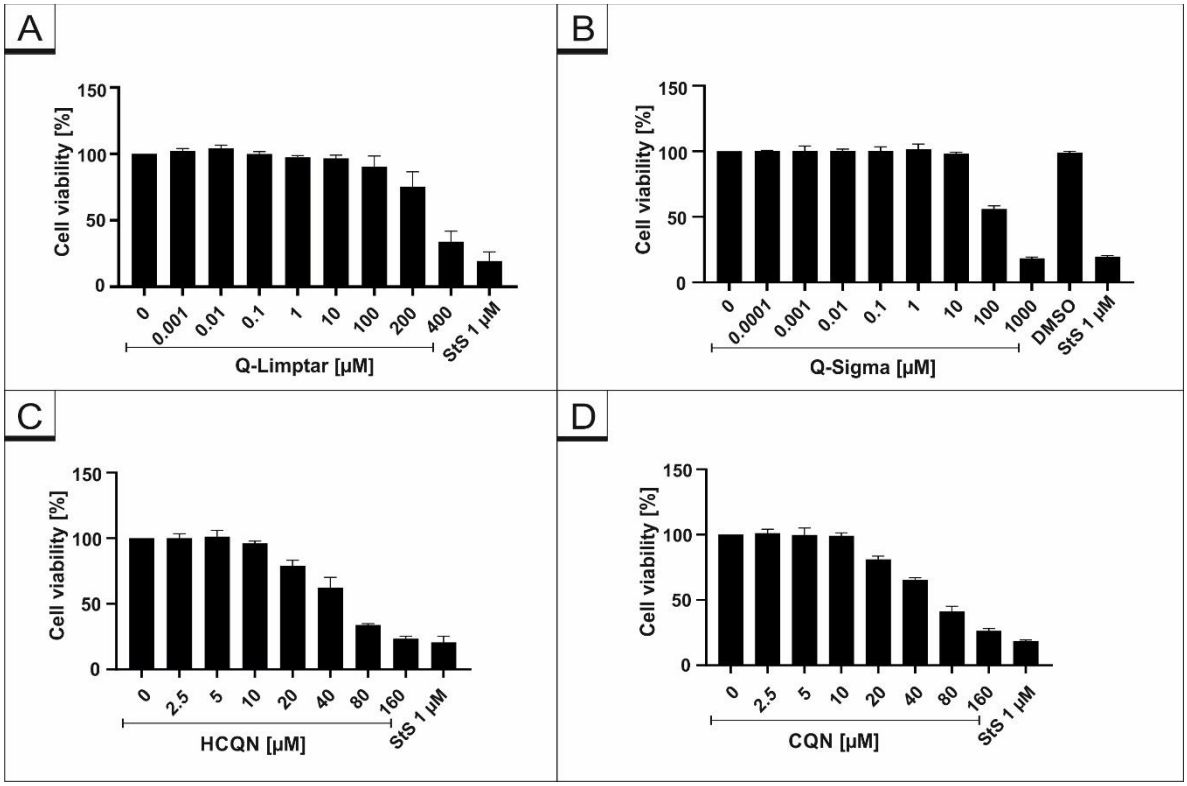


**Figure 2.** Influence of Quinine (A+B), H-CQN (C) and CQN (D) on the cell viability of Vero B4 cells. Following treatment for three days, the influence on cell viability was measured by water-soluble tetrazolium salt (WST)-1 assays. Quinine-sulfate was used as *Q-Limptar* (A) or *Q-Sigma* (B). Bars represent mean values of 3 independent experiments ±SD.

We next aimed to validate our findings from Vero cells in a SARS-CoV-2 permissive human cell system. For this, we employed human Caco-2 coloncarcinoma-derived epithelial cells. To facilitate the detection and analyses of infected cells, as well as to quantify viral spread in living cells we used the recently established SARS-CoV-2 infectious clone expressing mNeonGreen as reporter gene [36]. For a robust fluorescence readout we infected Caco-2 cells in 96-well plates with a relatively high MOI of 3. Then cells were treated with different amounts of Q-Limptar (Q-L) and Q-Sigma (Q-S). At 48 hpi cells were fixed and nuclei were stained with Hoechst in order to determine the relative infection rate (mNeonGreen+/Hoechst+ cells) as well as potential toxic effects of the treatment and infection (Fig. 3). This analysis confirmed our results obtained from Vero cells and suggests that concentrations up to 100 µM are non-toxic for Caco-2 cells (Fig. 3A). Furthermore, 50 µM and 100 µM Q-L or Q-S treatment inhibited SARS-CoV-2 infection at this high MOIs nearly completely, with a dose dependent effect down to 2 µM (Fig. 3 A and B).

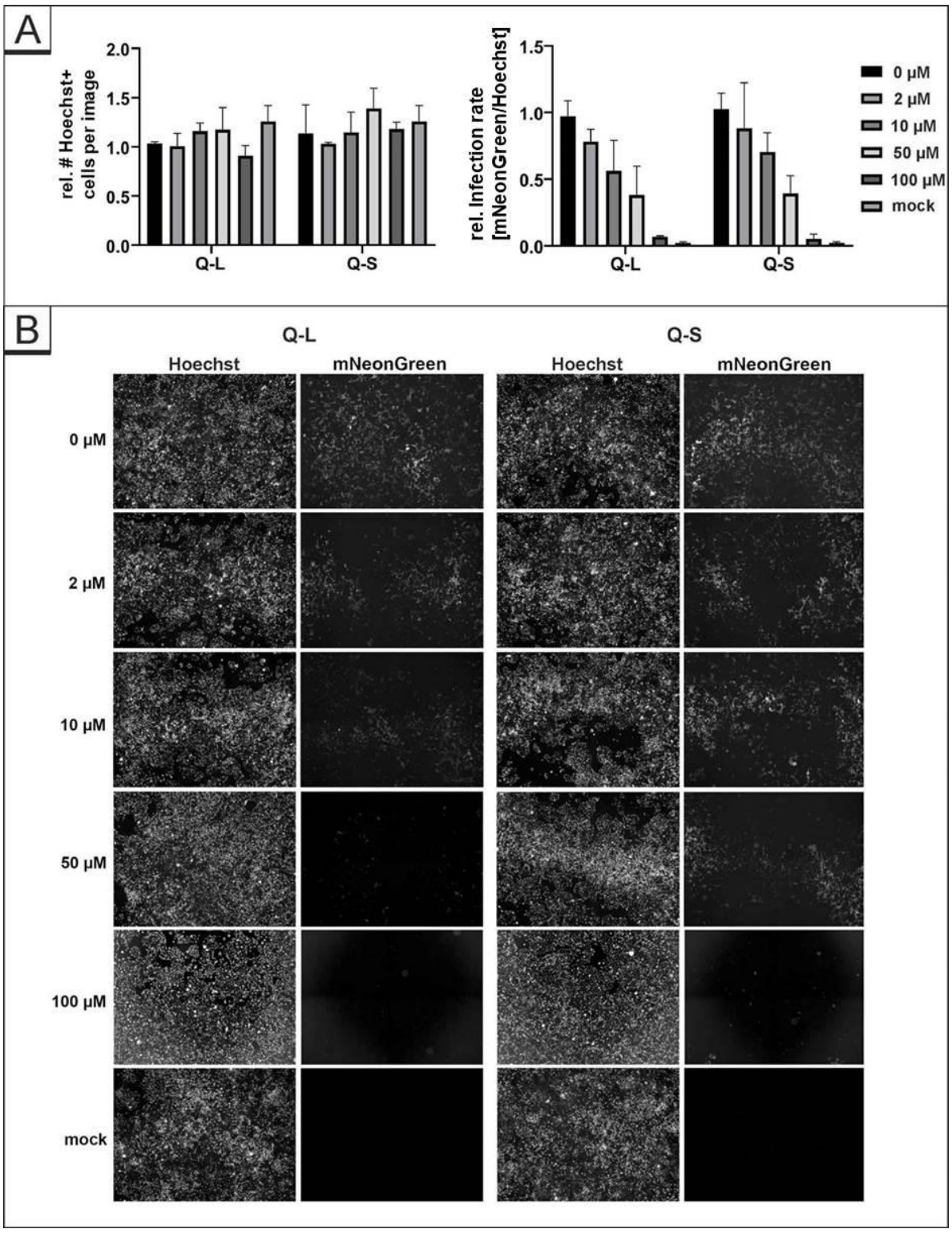


**Figure 3.** Influence of Quinine on SARS-CoV-2-mNG infection in Caco-2 cells. Cells were infected with SARS-CoV-2-mNG at a MOI of 3 for 1 hour or mock infected. Then the inoculum was removed and the cells were treated with the indicated amounts of *Q-Limptar* (Q-L) or *Q-Sigma* (Q-S). 48 hpi cells were fixed with 2% PFA and nuclei were stained with 1 µg/ml Hoechst. The total amount of cells (Hoechst+) and infected cells (mNeonGreen+) were analyzed by automated microscopy. (A) Quantitative analyses of total cells and infected cells. Mean values and SD are calculated from two experiments with duplicate infections. (B) Representative fluorescence microscopy images.

Taking advantage of the possibility to monitor viral spread in living cells, we imaged infected as well as Q-L/Q-S treated cells over a period of 48 hours in 1 hour intervals (Fig. 4). Of note, Quinine

treatment strongly delayed as well as suppressed viral spread and SARS-CoV-2 replication in Caco-2 cells (Fig. 4A and B as well as Supplemental Movies S1 and S2). Hence, Quinine seems to be effective against SARS-CoV-2 especially when administered early during infection. Altogether, the cumulated results suggest that Quinine exerts specific and dose-dependent decline in SARS-CoV-2 replication.

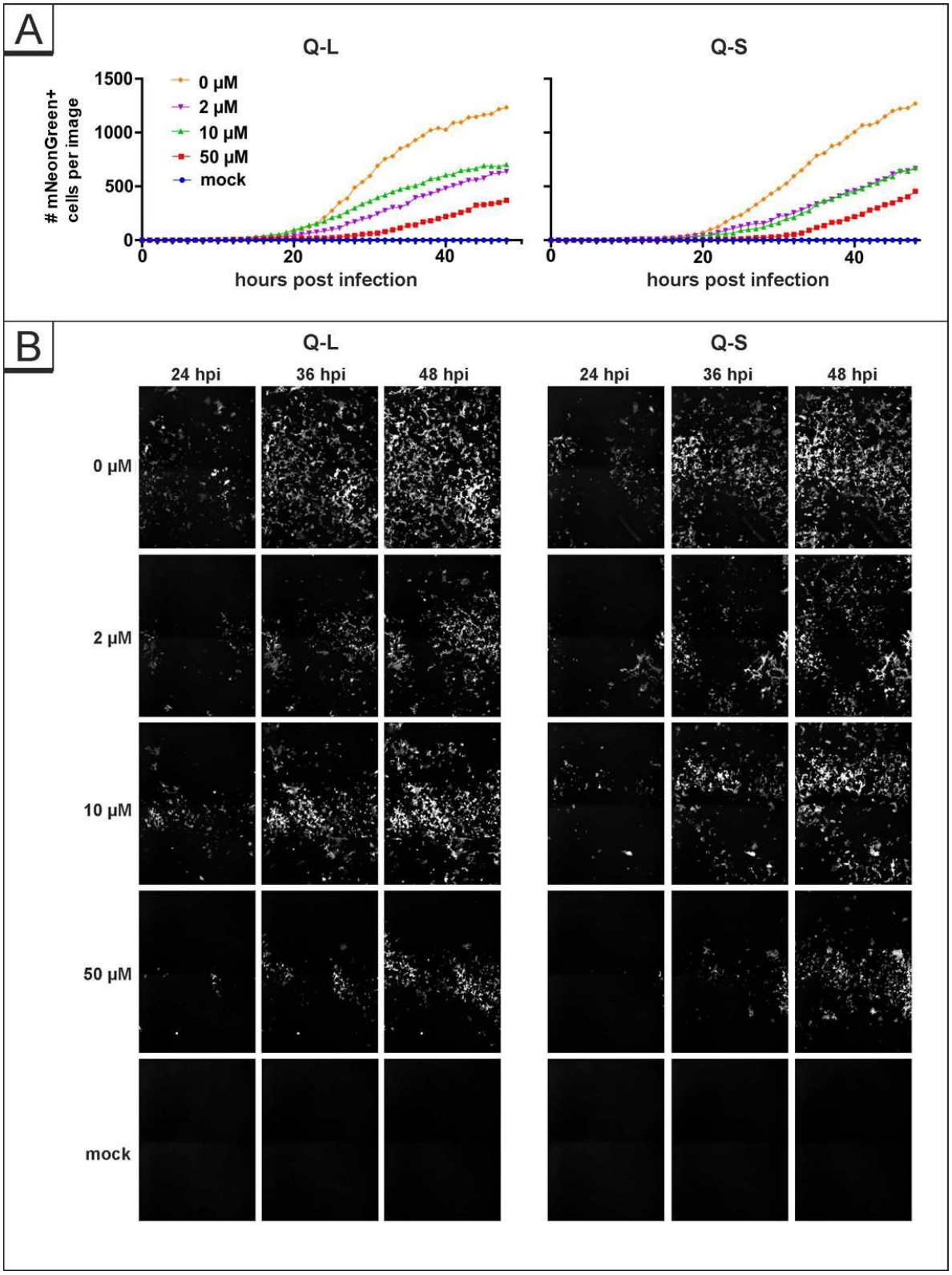


**Figure 4.** Influence of Quinine on the replication of SARS-CoV-2-mNG in Caco-2 cells. Similar experimental layout as described in the legend of Figure 3. However, cells were imaged every hour post removal of the virus and the amount of infected cells (mNeonGreen+) was analyzed by automated microscopy. (A) Quantitative analyses of the time course of viral replication as determined by the amount of mNeonGreen+

cells over 48 hours. (B) Representative fluorescence microscopy images for 24, 36 and 48 hpi of mNeonGreen+ i.e. SARS-CoV-2-mNG infected cells. The full-length time course analyses are available as supplemental videos (S1 and S2).

## 4. Discussion

We could show for the first time that the natural product Quinine exerts strong antiviral activity against SARS-CoV-2 infection. Currently, H-CQN and CQN are used as potential candidates in several clinical trials. However, there are major concerns due to severe side effects documented by conflicting results published so far [3, 10-22]. Based on the results of a recently published study [39], the WHO recommended a stop of clinical trials with H-CQN due to safety concerns on 27th of May 2020 [40, 41]. However, serious concerns raised about the reliability of this study and the publication was retracted soon later [42]. Due to this retraction, the WHO announced on 3rd of June 2020 that trials with H-CQN and CQN would now resume [43, 44]. Even though H-CQN may not have been able to meet the high expectations in clinical studies so far, its antiviral activity against SARS-CoV-2 should not be neglected, but pursued further in the search for effective drugs with a similar mode of action but a more promising toxicity profile. Due to the better pharmacokinetics, Quinine could meet exactly this challenge [9]. There are rudimentary, very first hints that Quinine and derivatives thereof are tested in clinical studies for their antiviral effect against SARS-CoV-2: In Indonesia health authorities are trialing Quinine as a possible treatment of COVID-19 [45]. In Russia the Federal Biomedical Agency wants to test the Quinine derivative Mefloquine in clinical trials [46]. However, scientific evidence for any potential antiviral activity of Quinine against SARS-CoV-2 has not been reported so far.

Medical analysis showed that high levels of cytokines in the plasma of patients correlate with a severe SARS-CoV-2 infection, assuming that an enhanced cytokine storm could be responsible for the need to transfer severe COVID-19 cases to an intensive care unit [1]. It was previously demonstrated that H-CQN and CQN have the ability to reduce the inflammatory response and thus have antipyretic activity [23]. Thus, also Quinine with a long-standing record as medication against feverish illnesses might be able to mitigate the cytokine storm associated with severe COVID-19. Considering our observation *in vitro* that Quinine exhibits an even higher antiviral effect than H-CQN or CQN, the natural product could replace H-CQN or CQN for treatment of COVID-19 patients due to a significant improvement in the toxicity profile.

In addition, as an approved aromatic agent, Quinine is added to bitter lemon and tonic water. According to EG-guidelines Nr. 1334/2008, Quinine-hypochloride (CAS-Nr. 130-89-2, Coe-Nr. 715), Quinine-sulfate (CAS-Nr. 804-63-7) or Quinine-monohydrochloride dehydrate (CAS-Nr. 6119-47-7) can be added to food or beverages [32]. Moreover, according to the well elaborated pharmacokinetics, 50-100 mg Quinine, present in 1 l of e.g. tonic water, could lead to a plasma concentration of ~0.5 µg/ml, which corresponds to a molarity of ~1.5 µM [47, 48], which would reach values that are effective in our *in vitro* systems. Additionally, H-CQN or CQN and Quinine have different pharmacokinetics. For instance, permanent therapeutic doses for Quinine results in a twenty times higher plasma concentration than for H-CQN [49-51]. At the beginning of a therapy with H-CQN or Quinine, a plasma molarity of ~150 nM can be achieved following treatment with 200 mg H-CQN and even a plasma molarity of 2.9 µM for treatment with 200 mg Quinine [52, 53]. While 200 mg H-CQN represents the common daily therapeutic dose, 200 mg Quinine is rather a low dose compared to the standard therapeutic range of this medication. As Quinine appears to exert a higher antiviral effect against SARS-CoV-2 with a significantly better toxicity profile *in vitro*, and has a predictable better plasma availability when compared to the controversially discussed drugs H-CQN and CQN, this natural product could pave the way to a more tolerable and widely used treatment of SARS-CoV-2 infections that might be even administered prophylactically.

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M.G., S.R., C.S.; writing—review and editing, U.S., M.S., N.R., R.B., M.G., C.S., S.R., E.B.; supervision, U.S., M.S.; funding acquisition, U.S., M.S. All authors have read and agreed to the published version of the manuscript.

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