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Evaluating the Clinical Failure of Oral Hydroxychloroquine in SARS-CoV-2 Treatment: A Systematic Literature Review Justifying the Potential for Inhaled Delivery

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ABSTRACT

A systematic review was conducted to summarize the evidence regarding the administration of hydroxychloroquine (HCQ) through oral and inhalation for treating SARS-CoV-2 infection during pandemic. We limit inclusion for studies evaluating the administration of oral or inhalation of HCQ monotherapy on infected person only. Most of the treatments were given via oral delivery and no evidence on HCQ inhalation for SARS-CoV-2 infected patients. Aside from 400 mg per day is the most common HCQ treatment dosage, majority of the studies highlighted that HCQ does not significantly contribute to reduction of new incident, severity, viral shedding time and mortality when compared with control group. Further study of inhaled HCQ is needed as this route of administration could offer a promising alternative to the current oral dosing regimens, potentially improving the therapeutic outcomes and reducing the risk of toxicity for patients.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the main causative virus contributing to the Coronavirus Disease 2019 (COVID-19) pandemic that initially emerged from China before it widely spread across the globe. SARS-CoV-2 known for sharing many similarities with SARS-CoV especially the amino acid sequences of Spike (S) proteins and the binding of the receptor-binding domain (RBD) of both virions to angiotensin-converting enzyme 2 (ACE2) receptor (Hasöksüz et al., 2020; W. Tai et al., 2020; Xu et al., 2020; P. Zhou et al., 2020) . Merad & Martin (2020) mentioned in their article that hyperinflammation due to SARS-CoV-2 might be a major contribution to the cause of disease severity and the fatal of infected patients, as well as to the association of cytokine storm which affecting the certain organs with abundance of ACE2 receptors. Due to the absence of effective medications for treating the infected patients, public health professionals have suggested the repurpose of available drugs to be used in managing the COVID-19 infection since it is a quick and efficient method for identifying new applications for medicines that already exist (Singh et al., 2020).

Early in the COVID-19 pandemic, hydroxychloroquine (HCQ) drew substantial attention as a potential COVID-19 treatment based on its antiviral and immunomodulatory effects in vitro. However, HCQ showed a lack of efficacy in vivo, and different groups of researchers attributed this failure to the insufficient drug concentration in the lung, following oral administration (HCQ is only available in the market in the tablet form during pandemic). However, some studies suggested that delivering HCQ by inhalation represents a more efficient route of administration to increase HCQ exposure in the lungs while minimizing systemic toxicity (Hawari et al., 2023). In addition, hydroxychloroquine sulfate (HCQ) administered as dry powder via inhalation could be safer than oral HCQ allowing higher and therefore more effective pulmonary concentrations without dose limiting toxic effects (de Reus et al., 2022). As reported by (The RECOVERY Collaborative Group (2020), despite the initial indications of the effectiveness of HCQ in smaller clinical studies, the efficacy of HCQ for patients diagnosed with COVID-19 has not been substantiated by extensive large-scale clinical trials.

HCQ is commonly administered via oral delivery, where the main issue is that the lungs are unable to achieve a good concentration of HCQ to kill coronavirus when the drug is delivered via oral (Alavi et al., 2020). Administration of drug via oral route typically results in slower absorption, in addition to the alteration of the drug stability and solubility due to the physiological environment in the gastrointestinal (GI) tract (Hua, 2020). The first-pass metabolism involves the absorption of the drug through GIT, and then into the liver via the enterohepatic circulation before being released into the systemic circulation (Maheshwari et al., 2018). This event will lead to the denaturation of oral drugs or hinder the drugs from being successfully absorbed by the target (Homayun et al., 2019). Therefore, it is suggested to deliver HCQ via inhalation directly into the lung in order to achieve desired drug concentration to kill SARS-CoV-2 virus.

Some studies proposed that direct application of the drug into the respiratory tract may increases the effectiveness of the treatment, at the same time, decreases the chances of overdose and toxicity (Fassihi et al., 2020; Kavanagh et al., 2020; Klimke et al., 2020). The results from the studies showed a similar positive outcome where the percentage of the concentration of the deposited HCQ in the lungs was higher when the drug delivered via inhalation, especially liposomal-HCQ-NPs, although the delivered dosage was low, compared to HCQ delivered via oral route. An optimal pharmacological targeting with low systemic exposure may be achieved through local delivery of drugs to the lungs (Eedara et al., 2021). When compared to oral medications, the inhaled treatments have a more immediate and direct effect on the respiratory zones, which suggests that they may have useful applications in the treatment of disorders that relate to respiratory issues (Taher et al., 2021). In fact, studies have proven that HCQ is safe and effective in treating other respiratory issues such as pulmonary sarcoidosis, and childhood interstitial lung disease (chILD) (McDonnell et al., 2011; Shaaban et al., 2021; Yavuz et al., 2021).

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HCQ administration via oral route for COVID-19 treatment is well-known despite variation of opinion on effective dosage. However, a knowledge gap that has picked the interest is concerning on the drug delivery via inhalation. Further understanding on this matter may result in new approach on controlling and treating the viral infection in more efficient way. Hence, in this systematic review, we assessed the efficacy and safety of current available oral and inhaled HCQ treatment monotherapy for SARS-CoV-2 infection.

METHODS

The systematic review (SR) was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The Joanna Briggs Institute (JBI) Critical Appraisal tool was followed for the process of critique or appraisal of the research evidence. This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY)(INPLASY202450029).

Search Strategy

A web-based search was carried out independently by three investigators (NSAZ, KHJ, AFMR) on three selected online database search engines (EBSCO, Scopus, and Web of Science) from January 2020 until June 2023. The search was conducted to include studies published in English language and containing keywords in the title abstract were selected. The search-terms used in various combinations of keywords mentioned in title or abstract were: “hydroxychloroquine”, “oral”, “inhal*”, and “SARS-CoV-2”. These keywords were then expanded by two-way synonyms to variant the terms with the same meaning. Therefore, we applied search features including Boolean operator, phrase searching, truncation, and wildcard on each database. Details of the search string for each database are annexed (Table 1).

Table 1. Search strategy.

Databases	Keywords used
EBSCO n = 1125	ALL((“hydroxychloroquine” OR “hidroxicloroquina” OR “hydroxychloroquinum” OR “oxichlorochine” OR “oxichloroquine”) OR (“oral”) OR (“inhal*” OR “aerosol*” OR “nebuliz*” OR “pulmonary delivery”) AND (“SARS-CoV-2” OR “COVID-19” OR “ACE-2 receptor”))
Scopus n = 911	ALL((“hydroxychloroquine” OR “hidroxicloroquina” OR “hydroxychloroquinum” OR “oxichlorochine” OR “oxichloroquine”) OR (“oral”) OR (“inhal*” OR “aerosol*” OR “nebuliz*” OR “pulmonary delivery”) AND (“SARS-CoV-2” OR “COVID-19” OR “ACE-2 receptor”))
Web of Science n = 14	ALL((“hydroxychloroquine” OR “hidroxicloroquina” OR “hydroxychloroquinum” OR “oxichlorochine” OR “oxichloroquine”) OR (“oral”) OR (“inhal*” OR “aerosol*” OR “nebuliz*” OR “pulmonary delivery”) AND (“SARS-CoV-2” OR “COVID-19” OR “ACE-2 receptor”))

Eligibility Criteria

Studies were included if: (1) reporting data on hydroxychloroquine for SARS-CoV-2 infection treatment; (2) focused on oral or inhale deliveries; (3) the full text was available. We excluded studies focusing on treatment with hydroxychloroquine combination with other drugs, in any form of drug deliveries, as well as the use of hydroxychloroquine for treatments other than SARS-CoV-2.

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A pre-design data extraction form was used to extract information on the following: study design, number of patients (HCQ-treated and control), exposure, control, adverse events related to drug application, outcome of the study, and the limitation of the study. The inclusion and exclusion criteria are stated in Table 2.

Table 2. Inclusion and exclusion table.

PICO	Inclusion	Exclusion
Population	SARS-CoV-2 infected patients, or those who continuously or recently close-contact exposure to positively COVID-19 patients.	Healthy volunteers.
Intervention/Exposure	HCQ monotherapy either via oral or inhalation deliveries for SARS-CoV-2 treatment.	Administration of HCQ monotherapy or with the combination of other drugs through different or same types of medicinal delivery.
Comparison	The effect of HCQ treatment on the COVID-19 progress, between oral and inhalation drug delivery.	
Outcome	Effects generated by HCQ treatment via oral or inhalation deliveries on the viral progression.	Effects generated by HCQ monotherapy or with the combination of other drugs via different or same types of medicinal deliveries on the viral progression.
Literature type	Reports must contain original data.	Journals with no original data (e.g., reviews, editorials, letters, book chapters, notes, conference papers, short surveys, case reports, guidelines, comparative studies, congress, etc.) Languages other than English

Study Selection, Screening Process and Data Extraction

Titles and abstracts of the studies that were retrieved were screened by three investigators, (NSAZ, KHJ, AFMR) and after that, publications that met the inclusion criteria were determined. The reviewing authors were able to address their disagreements with one another through a thoughtful conversation, and any residual conflicts were resolved by the other two reviewers (NEAR, NAHM). Following that, the full texts of the eligible articles were retrieved. Finally, using the inclusion criteria as a guide, three reviewers (NSAZ, KHJ, AFMR), screened and chose the relevant full-text publications independently of one another. The disagreements between the writers who performed the reviews were settled using the same method that was applied during the initial phase of selection.

On the next available time, the other three reviewers (NSAZ, KHJ, AFMR) extracted the following data out of the articles: year, study design, number of patients (HCQ-treated and control), exposures, control, adverse events, outcomes, and limitations of the study.

Assessment of Reliability

Using the Joanna Briggs Institute (JBI) Critical Appraisal tools which was developed by the JBI and collaborators (Aromataris et al., 2015), the reliability assessment was carried out independently by four reviewers (SM, RY, MA, YH). The reliability was evaluated according to nine criteria, each yielding a score of zero or one. One score was obtained for each criterion if the study was affirmative in the next

questions: (1): Was the sample frame appropriate to address the target population? (2): Were study participants sampled in an appropriate way? (3): Was the sample size adequate? (4): Were the study subjects and the setting described in detail? (5): Was the data analysis conducted with sufficient coverage of the identified sample? (6): Were valid methods used for the identification of the condition? (7): Was the condition measured in a standard, reliable way for all participants? (8): Was there appropriate statistical analysis? (9): Was the response rate adequate, and if not, was the low response rate managed appropriately?

Any clash in agreements that arose between the authors were resolved through discussion, or by further discussion with the fifth and sixth reviewer (ST, NAHM).

RESULTS

Study Selection

Our initial web-based search identified 2050 literatures, comprising 1125 titles from EBSCO, 911 from Scopus and 14 from Web of Science; the searches included literature published up to June 2023. From these literatures, an additional 22 titles yielded through snowballing approach. Primary screening based on literature document types; only peer-reviewed scientific papers included in the study, resulting in the exclusion of 1351 titles. Next screening was done by excluding the literatures based on title and abstract that does not meet the eligibility criteria. Then, the full-text screening excluded 74 articles due to off-topic, and another 2 articles were removed since they are duplicated. A total of 26 studies were included in this systematic literature review, corresponding to 26 HCQ oral administrated studies and based until this work is published, no publication was identified HCQ as the route of administration in the management of SARS-CoV infections (Figure 1 PRISMA flow diagram).

Among the total publications (n=26) obtained using the MESH terms for HCQ administration during COVID-19 pandemic, majority of the reported articles were the randomized control trial (n= 19) (Avezum et al., 2022; Barnabas et al., 2021; Barratt-Due et al., 2021; Boulware et al., 2020; Cavalcanti et al., 2020; C.-P. Chen et al., 2020; Hernandez-Cardenas et al., 2021; Johnston et al., 2021; Khamis et al., 2020; Mitjà et al., 2020, 2021; Prasad Dhibar et al., 2023; Reis et al., 2021; Schwartz et al., 2021; Self et al., 2020; Skipper et al., 2020; Tang et al., 2020; The RECOVERY Collaborative Group, 2020), retrospective studies (n=3) (Arshad et al., 2020; Choi et al., 2021; Nagaraja et al., 2020), observational studies (n=1) (Bitaraf et al., 2021; Catteau et al., 2020), and only one article is reported as non-randomised study (Agusti et al., 2022) while one clinical trial of oral administration of HCQ was reported by Ader et al. (2021). However, Ucan et al. (2020) reported a retrospective observational case-controlled study which means 144 the sample population used. No articles report on administration of HCQ monotherapy via inhalation for SARS-CoV-2 infected patients available and included in this study. None of the articles also mentioned about the vaccination status of the patients. All included articles we undergone JBI Critical Appraisal assessment resulting 11 high quality studies, while the rest of the included studies were in moderate quality (Table 3).

In terms of the subjects or patients that received the HCQ administration, five studies were conducted for hospitalized patients with moderate to severe infection (Ader et al., 2021; Hernandez-Cardenas et al., 2021; Khamis et al., 2020; Ucan et al., 2020) and six studies described the administration of oral HCQ for mild to moderate hospitalised patients infected with SARS-CoV-2 (Bitaraf et al., 2021; Catteau et al., 2020; Cavalcanti et al., 2020; C.-P. Chen et al., 2020; Choi et al., 2021; Self et al., 2020; The RECOVERY Collaborative Group, 2020) and one study by Tang et al. (2020) reported patients enrolment and administration of oral HCQ for mild, moderate and severe patients.

Meanwhile in the non hospitilised patients, six articles (Agusti et al., 2022; Avezum et al., 2022; Johnston et al., 2021; Mitjà et al., 2020; Reis et al., 2021; Schwartz et al., 2021; Skipper et al., 2020) reported the treatment of HCQ was prescribed to patients with mild to moderate SARS-CoV-2 infection. However, three articles analysed on the administration of HCQ for post-exposure patients with either individuals with history of high-risk status and direct contacts with COVID-19 case (Prasad Dhibar et al., 2023), cluster-randomized trial involving asymptomatic contacts of patients with positive PCR (Mitjà et

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al., 2021) and persons who were at risk for SARS-CoV-2 infection and subsequently demonstrated high incidence and close contact with people who were positive with SARS-CoV-2 infection (Barnabas et al., 2021). The administration of HCQ for pre-exposure healthcare workers (HCW) was reported by Nagaraja et al. (2020).

Table 3: JBI Critical Appraisal assessment.

No.	Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Score	Quality
1.	Prasad Dhibar et al. (2023)	YES	YES	YES	YES	YES	YES	YES	YES	YES	100%	HIGH
2.	Avezum et al. (2022)	YES	YES	NO	YES	YES	YES	YES	YES	YES	88.89%	HIGH
3.	Agusti et al. (2022)	YES	YES	NO	YES	YES	YES	NO	NO	YES	66.67%	MODERATE
4.	Khamis et al. (2020)	YES	YES	NO	YES	YES	YES	NO	YES	YES	77.78%	MODERATE
5.	Choi et al. (2021)	YES	YES	YES	YES	YES	YES	NO	NO	YES	77.78%	MODERATE
6.	Ucan et al., 2020)	YES	YES	NO	YES	YES	YES	NO	NO	YES	66.67%	MODERATE
7.	Bitaraf et al. (2021)	YES	YES	YES	YES	YES	YES	NO	NO	NO	66.67%	MODERATE
8.	Reis et al. (2021)	YES	YES	NO	YES	YES	YES	YES	YES	YES	88.89%	HIGH
9.	Schwartz et al. (2021)	YES	YES	NO	YES	YES	YES	YES	NO	YES	77.78%	MODERATE
10.	Johnston et al. (2021)	YES	YES	YES	YES	YES	YES	NO	YES	YES	88.89%	HIGH
11.	Mitjà et al. (2020)	YES	YES	NO	YES	YES	YES	NO	YES	YES	77.78%	MODERATE
12.	Hernandez-Cardenas et al. (2021)	YES	YES	NO	YES	YES	YES	YES	YES	YES	88.89%	HIGH
13.	Ader et al. (2021)	YES	YES	NO	YES	YES	YES	NO	YES	YES	77.78%	MODERATE
14.	Barratt-Due et al. (2021)	YES	YES	NO	YES	YES	YES	NO	YES	YES	77.78%	MODERATE
15.	Nagaraja et al. (2020)	YES	YES	NO	YES	YES	NO	NO	YES	YES	66.67%	MODERATE
16.	Skipper et al. (2020)	YES	YES	YES	YES	YES	NO	YES	YES	NO	77.78%	MODERATE
17.	Mitjà et al. (2021)	YES	YES	YES	YES	YES	YES	NO	YES	YES	88.89%	HIGH
18.	Boulware et al. (2020)	YES	YES	YES	YES	YES	NO	YES	YES	YES	88.89%	HIGH
19.	Barnabas et al. (2021)	YES	YES	PARTIAL	YES	YES	YES	YES	YES	YES	88.89%	HIGH
20.	Self et al. (2020)	YES	YES	NO	YES	YES	YES	YES	YES	YES	88.89%	HIGH
21.	The RECOVERY Collaborative Group (2020)	YES	YES	YES	YES	YES	YES	NO	YES	YES	88.89%	HIGH
22.	Cavalcanti et al. (2020)	YES	YES	YES	YES	YES	YES	NO	YES	YES	88.89%	HIGH
23.	Catteau et al. (2020)	YES	YES	YES	YES	YES	YES	NO	NO	NO	66.67%	MODERATE
24.	Arshad et al. (2020)	YES	YES	YES	YES	YES	YES	NO	NO	YES	77.78%	MODERATE
25.	Tang et al., 2020)	YES	YES	NO	YES	YES	YES	NO	YES	YES	77.78%	MODERATE

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26.	C.-P. Chen et al. (2020)	YES	YES	NO	YES	YES	YES	NO	NO	YES	66.67%	MODERATE

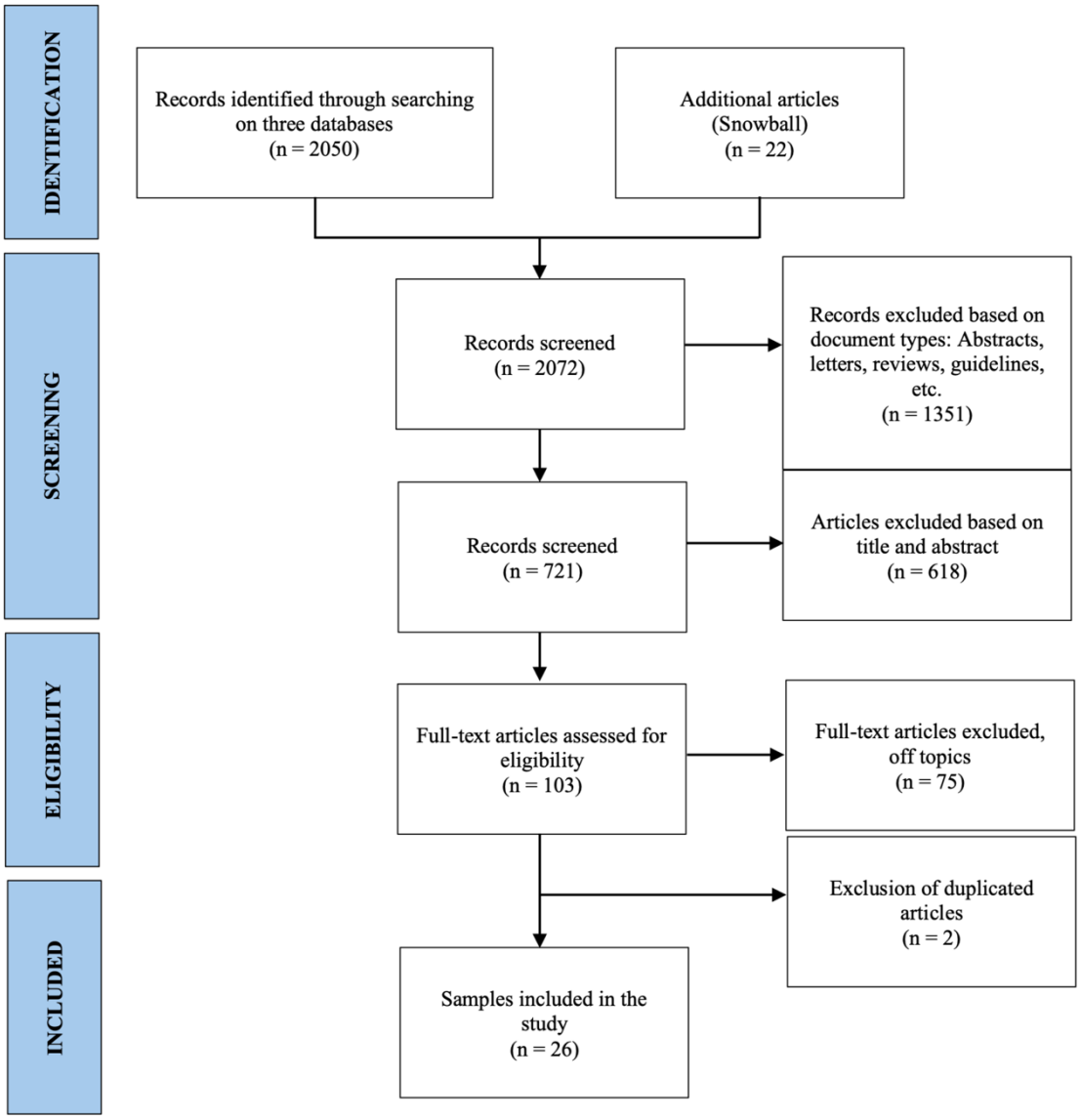

Figure 1: PRISMA flow diagram for identification of relevant study.

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Table 4: HCQ oral delivery.

Author (Year)	Study Design	Patient Care	Number of Patient		Severity of Infection	Intervention/ Exposure	Primary Outcome	Secondary Outcome
			HCQ	Control				
Prasad Dhibar et al. (2023)	Randomized Controlled Study	Non-Hospitalized	574	594	Post-Exposure	HCQ 400 mg q 12 hourly on day one, followed by 400 mg once weekly for 3 weeks (total 5 tablets and collective dose of 2000 mg	The incidence of definite and probable COVID-19 cases	Clinical status
Avezum et al. (2022)	Randomized Controlled Study	Non-Hospitalized	689	683	Mild/ Moderate	HCQ 400 mg (BID) on day 1, 400 mg (OD) for 7 days	The incidence of hospitalizatio n within 30 days	Clinical status on day 30
Agusti et al. (2022)	Non-Randomized Study	Healthcare Workers	87	55	Mild	HCQ at baseline for five days, with a loading dose of 400 mg q12 h the first day, followed by 200 mg q12 h the remaining four days	PCR negative on day 7	Time to negative conversion of PCR, and clinical status
Khamis et al. (2020)	Randomized Controlled Study	Hospitalized	45	44	Moderate/ Severe	HCQ 400 mg twice per day on day 1, then 200 mg twice per day for 7 days.	Time to clinical recovery, the normalization of inflammatory markers and improvement in oxygen saturation that is maintained for at least 72 h	Clinical status within 14 days
Choi et al. (2021)	Retrospective Case-Controlled Study	Hospitalized	801	2128	Mild/ Moderate	HCQ 400 mg/d (200 mg/bid) for 5-6 days	Duration of viral shedding	Not Reported
Ucan et al. (2020)	Retrospective Observational Case-Controlled Cohort Study	Hospitalized	48		Mild/Mode rate/Severe/ Critical	Not Reported	PCR negative	The rate of admission to an ICU and the rate of death.
Bitaraf et al.)2021)	Observational Study	Hospitalized	20	16	Mild/ Moderate	Not Reported	The incidence of death and length of stay (LOS)	Not Reported

(Reis et al. (2021)	Randomized Controlled Study	Non-Hospitalized	214	227	Mild/ Moderate	HCQ 800 mg loading dose, 400 mg daily for 9 days	The incidence of hospitalizatio n and death at 90 days	Clinical status and viral load at day 3, 7, and 14
Schwartz et al. (2021)	Randomized Controlled Study	Non-Hospitalized	111	37	Mild/ Moderate	HCQ 400 mg (BID) on day 1, 200 mg (BID) for 4 days, or identical matching placebo (12 tablets over 5 days)	The incidence of hospitalizatio n, invasive mechanical ventilation, or death within 30 days	Clinical status within 30 days
Johnston et al. (2021)	Randomized Controlled Study	Non-Hospitalized	71	83	Mild/ Moderate	HCQ 400 mg (or AA 500 mg) twice on Day 1, followed by HCQ 200 mg (or AA 250 mg) twice daily for 9 days plus AZ 500 mg (or FA 800 µg) once on Day 1, followed by AZ 250 mg (or FA 400 µg) once daily for 4 days.	Viral load, development of lower respiratory tract infection (LRTI) through Day 14, incidents of hospitalizatio n for Covid-19 or death	Clinical status
Mitjà et al. (2020)	Randomized Controlled Study	Non-Hospitalized	169	184	Mild/ Moderate	HCQ 800 mg on Day 1, 400 mg OD for 6 days	Viral load at days 3, and 7	Clinical status
Hernande z-Cardenas et al. (2021)	Randomized Controlled Study	Hospitalized	106	108	Severe	HCQ 200 mg every 12 h, for 10 days	30 days mortality rate	Clinical status
Ader et al. (2021)	Clinical Trial	Hospitalized	145	148	Moderate/ Severe	HCQ 400 mg orally, twice on day 1 as a loading dose followed by 400 mg once daily for 9 days	Clinical status at 14 days	Clinical status at day 29 and the time to an improveme nt of two categories
Barratt-Due et al. (2021)	Randomized Controlled Study	Hospitalized	52	54	Mild/ Moderate	800 mg of oral HCQ twice daily on day 1, then 400 mg twice daily up to 9 days	In-hospital mortality	Clinical status

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Nagaraja et al. (2020)	Retrospective Cross-Sectional Study	Healthcare Workers	166	-	Pre-exposure	HCQ 400 mg twice daily on Day 1 followed by 400 mg weekly for 7 weeks	Adverse event profile, practice and precautionary measures taken prior to and during hydroxychloroquine therapy.	Not Reported
Skipper et al. (2020)	Randomized Controlled Study	Non-Hospitalized	212	211	Mild/ Moderate	HCQ 800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 more days	Clinical status within 14 days	The incidence of hospitalization for Covid-19 or death, clinical status at day 5 and day 14 and incidence of study medicine withdrawal
Mitjà et al. (2021)	Randomized Controlled Study	Non-Hospitalized	1116	1198	Post-exposure	HCQ 800 mg on day 1, followed by 400 mg once daily for 6 days	PCR positive, symptomatic Covid-19 episode	The incidence of hospitalization for Covid-19 or death
Boulware et al. (2020)	Randomized Clinical Study	Non-Hospitalized	414	407	Not Reported	HCQ 800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) daily for 4 more days for a total course of 5 days (19 tablets total	PCR positive, symptomatic Covid-19 episode	The incidence of hospitalization for Covid-19 or death, PCR positive, the incidence of Covid-19 symptoms, clinical status
Barnabas et al. (2021)	Randomized Controlled Study	Non-Hospitalized	407	422	Post-exposure	HCQ 400 mg/d for 3 days followed by 200 mg/d for 11 days	PCR positive among negative patients at baseline	Clinical status

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Self et al. (2020)	Randomized Controlled Study	Hospitalized	242	237	Mild/ Moderate	HCQ (400mg twice daily for 2 doses, then 200mg twice daily for 8 doses	Clinical status 14 days	Clinical status, including 28-day mortality
The RECOVERY Collaborative Group 2020)	Randomized Clinical Trial	Hospitalized	1561	3155	Mild/ Moderate	Not Reported	All-cause mortality within 28 days	Clinical status
Cavalcanti et al. (2020)	Randomized Controlled Study	Hospitalized	221	227	Mild/Moderate	HCQ 400 mg/bid for 7 day	Clinical status at 15 days	Clinical status at 7 days
Catteau et al. (2020)	Observational Study	Hospitalized	4542	3533	Mild/Moderate	HCQ 2400 mg in total over 5 day	Discharge status (survivors versus non-survivors	Treatment group (HCQ versus no-HCQ
Arshad et al. (2020)	Retrospective Cohort Study	Hospitalized	1202	409	Not Reported	HCQ 800 mg (400 mg/bid) on day 1, followed by 400 mg (200 mg/bid)	In-hospital mortality	Not Reported
Tang et al. (2020)	Randomized Controlled Study	Hospitalized	75	75	Mild/Moderate/Severe	Hydroxychloroquine administrated at a loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily (total treatment duration: two or three weeks for patients with mild to moderate or severe disease, respectively).	PCR negative within 28 days and clinical improvement among severe patients by 28 days	PCR negative at day 4, 7, 10, 14, or 21
C.-P. Chen et al. (2020)	Randomized Controlled Study	Hospitalized	21	12	Mild/Moderate	HCQ administration plan was 400 mg b.i.d. on day 1 and 200 mg b.i.d. for 6 days on days 2–7	PCR negative	PCR negative on day 14, clinical status and the mortality rate.

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Dose of Administration

The dose of administration was found to be varies at different studies. For hospitalized patients with moderate to severe infection state, the loading dose of 400 mg twice a day in Day 1 followed by a maintenance dose of 400 mg daily for 7 days of treatment as reported by Khamis et al. (2020), whereas Ader et al. (2021) reported the same maintenance dose for 9 days of treatment window. The same loading and maintenance doses were reported to be administered among hospitalized patients with mild to moderate infection state (C.-P. Chen et al., 2020; Self et al., 2020), whereas Cavalcanti et al. (2020) reported a constant administration of HCQ dosage of 400 mg twice daily for 7 days of treatment.

On the contrary, a continuous dosage of 200 mg twice a day for hospitalized patients with mild to moderate infection state was reported by Choi et al. (2021); for 5 to 6 days of treatment window, and Hernandez-Cardenas et al. (2021); for 10 days of treatment window. A loading dose of 800 mg twice a day in Day 1 followed by a maintenance dose of 400 mg twice daily for 9 days treatment was reported by Barratt-Due et al. (2021). Tang et al. (2020) reported administration of a loading dose of 1200 mg daily for 3 days followed by a maintenance dose of 800 mg daily for 2 weeks for patients with mild to moderate infection state and 3 weeks of total treatment duration for severe infected patients.

The loading dose of 800 mg in Day 1 followed by 400 mg of maintenance dose was reported to be administered among non-hospitalized patients (Avezum et al., 2022; Johnston et al., 2021; Mitjà et al., 2020; Reis et al., 2021; Schwartz et al., 2021). The difference between the studies reported was the total of treatment durations for the maintenance dose; 4 days (Schwartz et al., 2021), 6 days (Mitjà et al., 2020), 7 days (Avezum et al., 2022), and 9 days (Johnston et al., 2021; Reis et al., 2021). An identical loading and maintenance doses were also reported for HCQ treatment among COVID-19 infected healthcare workers (Agusti et al., 2022). Boulware et al. (2020) and Skipper et al. (2020) reported the same dosing instruction of a total 5-day course, where the loading dose of 800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 days.

As for the administration of HCQ for post-exposure patients, a loading dose of 800 mg in Day 1 followed by 400 mg of maintenance dose for 6 days of treatment window reported by Mitjà et al. (2021) whereas Prasad Dhibar et al. (2023) reported the same maintenance dose but once weekly for 3 weeks. Barnabas et al. (2021) reported a loading dose of HCQ 400 mg once for 3 days followed by 200 mg once for 11 days.

Hydroxychloroquine for Prophylaxis

For non-hospitalized patients, three articles discussed on the clinical intervention of HCQ administration as the prophylaxis agent. Prasad Dhibar et al. (2023) reported post-exposure prophylaxis among healthcare workers (HCW) with HCQ was not associated with significant reduction in incidence of new onset COVID-19 as compared to the placebo. All outcomes showed no significant differences between HCQ group and control group despite the number of HCW with definite COVID-19 and new onset symptoms in HCQ group were lower (2.8%; 3.0%) than control group (3.5%; 4.0%). Meanwhile, Barnabas et al. (2021) reported 53 new incidences of SARS-CoV-2 infection detected among patients who received HCQ as the prophylaxis treatment compared to 45 new incidences in the control group which were detected in the first 14 days of follow-up. Mitjà et al. (2021) reported patients who were close contacts with persons with confirmed SARS-CoV-2 infection have higher probability of getting a symptomatic COVID-19 compared to contacts those who had a negative PCR (20.4% vs 3.7%). According to all these three studies, there were no significant changes observed among the participants who received HCQ as the prophylaxis treatment. Indeed, some studies reported cardiac disorder (e.g. palpitations), however, the most common treatment-related side effects were gastrointestinal and nervous system disorders.

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Hospitalization and death

Studies of HCQ treatment on non-hospitalized SARS-CoV-2 infected patients revealed that the medication were insignificantly reduce the risk of hospitalization (Avezum et al., 2022; Mitjà et al., 2021; Reis et al., 2021). Johnston et al. (2021) reported one of the patients who received HCQ alone treatment from high-risk and low-risk groups had COVID-19 related hospitalization. The same for Schwartz et al. (2021), four patients in the HCQ group were hospitalized due to SARS-CoV-2 infection. However, the reported hospitalization was all due to pneumonia from the infection; none were related to treatment.

Although there were studies reported no death related to HCQ, some of the available researches highlighted that the treatment did not show any significant effect in reducing the rate of mortality when compared with the control group (Bitaraf et al., 2021; Hernandez-Cardenas et al., 2021; Johnston et al., 2021; Self et al., 2020; The RECOVERY Collaborative Group, 2020; Ucan et al., 2020). Patients with severe and hypoxemic subset of COVID-19 did not significantly benefit from HCQ in terms of 30-day mortality (Hernandez-Cardenas et al., 2021). Aside from that, patients who received HCQ had a higher chance of dying from cardiac causes (mean [SE] excess, 0.4±0.2 percentage points) and from non-COVID-19 related (mean excess, 0.4±0.2 percentage points)(The RECOVERY Collaborative Group, 2020).

On the other hand, study by Arshad et al. (2020) reported survival advantage exerted by HCQ. Based on the result from multivariate Cox regression model of mortality using control group as reference, treatment with HCQ monotherapy reduced the mortality hazard ratio by 66% ($p < 0.001$). In addition, the study also revealed that the hydroxychloroquine-treated group had considerably superior survival, and this improved survival persisted for up to 28 days after admission.

HCQ Administration to Reduce the Viral Shedding

From our study, it was notably found that for articles discussed on the impact of viral shedding upon administration of HCQ. All the seven articles suggested that administration of HCQ for SARS-CoV-2 infection treatment did not demonstrate any advantages in shortening the viral shedding time (Agusti et al., 2022; C.-P. Chen et al., 2020; Choi et al., 2021; Johnston et al., 2021; Mitjà et al., 2021; Reis et al., 2021; Tang et al., 2020; Ucan et al., 2020). Agusti et al. (2022) reported that the percentage of patients with negative viral load was numerically higher in the HCQ group than in the control group; however, no differences were statistically significant. Despite in the initial analysis HCQ group showed 62% faster in virologic clearance, the medication treatment was no longer significantly associated with shortening time to viral clearance in later model analyses ($p = 0.126$ and $p = 0.55$) (Johnston et al., 2021).

DISCUSSION

The transmission of SARS-CoV-2 virus occurs primarily through respiratory droplets and aerosols generated during coughing or sneezing which leads the virus to travel directly into the respiratory tract of the host and initiates lung damage (L. Zhou et al., 2021). This can be seen as one of the most common causes of COVID-19 patient's fatality is respiratory failure due to COVID-19 pneumonia leading to acute respiratory distress syndrome (ARDS) (Estenssoro et al., 2022; Sagoschen et al., 2022). Due to this concern, drug delivery to the infected site is important to ensure the effectiveness of the drug, especially to maximize the antiviral activity exerted by the drug against the virus. However, dosage regimen should not be overlooked since the correct dosage regimen is important for achieving desired therapeutic efficacy and avoiding undesired effects (Maheshwari et al., 2018). Unlike oral administration, drug administration via inhalation can rapidly boost high-effective local drug concentration at the site of action and at the same time minimize the side effects for treating respiratory conditions (Dhanani et al., 2022).

As we can observe in Table 3, most of the usage of HCQ for COVID-19 treatment was given via oral administration. The oral drug delivery is known as the most favored and preferred route of drug delivery in pharmaceutical, due to its advantages, such as well-established delivery system, non-invasive drug delivery, manageable drug's prescription, ease of administration, convenient for self-administration, as well as

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patient compliance (Homayun et al., 2019; Hua, 2020; Patel et al., 2018). Although HCQ displayed good results in some studies; however, there were also studies revealed that patients treated with HCQ did not: (i) improve the viral clearance; (ii) improve symptoms severity; and (iii) benefits in preventing SARS-CoV-2, when compared to the control group. This may happen due to the lack efficacy of HCQ when given orally (Kolli, Calvino-Martin, et al., 2022). In fact, there is a possibility that the lungs are unable to achieve a good concentration of HCQ to kill coronavirus when the drug is delivered via oral (Alavi et al., 2020).

Despite all the advantages offered by oral drug administration, it is also well-known for its challenges in absorption mechanism (Homayun et al., 2019). The acknowledge presence of the physical barriers (mucous layer, epithelial membrane components, and efflux transporter), biochemical barriers (enzymes), first-pass metabolism, and intestinal lymphatic transport (Azman et al., 2022) along the small intestine, resulting the insufficient of the drug to reach and absorb into the systemic circulation, leading to the low plasma drug concentration and low drug bioavailability. Thus, the insufficient concentration of the drug to the target site will hinder the antiviral activity of the drug against the virus.

Another possible reason for the conflicting results is that the optimal dosing regimen of HCQ for treating COVID-19 remains unclear, and effective *in vivo* levels of HCQ may not be achievable. T. T. Tai et al. (2021) proposed the *in vitro* half-maximal effective concentration values is needed (0.72-17.31 μM) for optimized dosing regimens based on extracellular drug concentrations. However, modeling suggested that a higher lung (intracellular) concentration may be required for *in vivo* antiviral efficacy. The HCQ concentration (6.900 ng/mL) required to clear 100% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *in vitro* might not be achievable in lung with the currently proposed oral dosing regimen of 800 mg HCQ sulfate orally daily, followed by a maintenance dose of 400 mg given daily for 4 days (Yao et al., 2020). To achieve an effective antiviral HCQ concentration in the lungs, higher cumulative doses of HCQ are required for oral administration, raising concerns of systemic toxicity, including cardiotoxicity (Fernandez-Ruiz et al., 2020; Mubagwa, 2020).

Compared to the oral drug delivery, the inhalation drug therapy delivers the drug directly to the lung to induce the therapeutic effect (He et al., 2022). The benefits of inhalation administration above particularly relied on: the large surface area for absorption, a thin alveolar epithelial cell membrane, high permeability, fast absorption; low enzyme activity to prevent the liver's first-pass effect; and maintenance of high therapeutic concentrations at the target site, making the inhalation of drug is preferable for treatment targeting the lungs (He et al., 2022).

Despite the aforementioned advantages of this type of pharmaceutical therapy, similar to the challenges upon oral drug administration, the respiratory system possesses a complex yet comprehensive array of defenses against inhaled particles. The drugs delivered via inhalation are exposed to multiple clearance mechanisms and/or barriers in the respiratory tract including, mucociliary clearance (responsible in expulsion of drug and mucus out of respiratory tract), pulmonary surfactant (involve in removal of drugs), immune cells (involved in endocytosis activation, preventing the absorption of inhaled drugs), enzymes (involve in degradation and metabolism of drugs), and biofilm (involve in drug interaction with the biofilm, resulting to the decrease of drug efficacy) (He et al., 2022).

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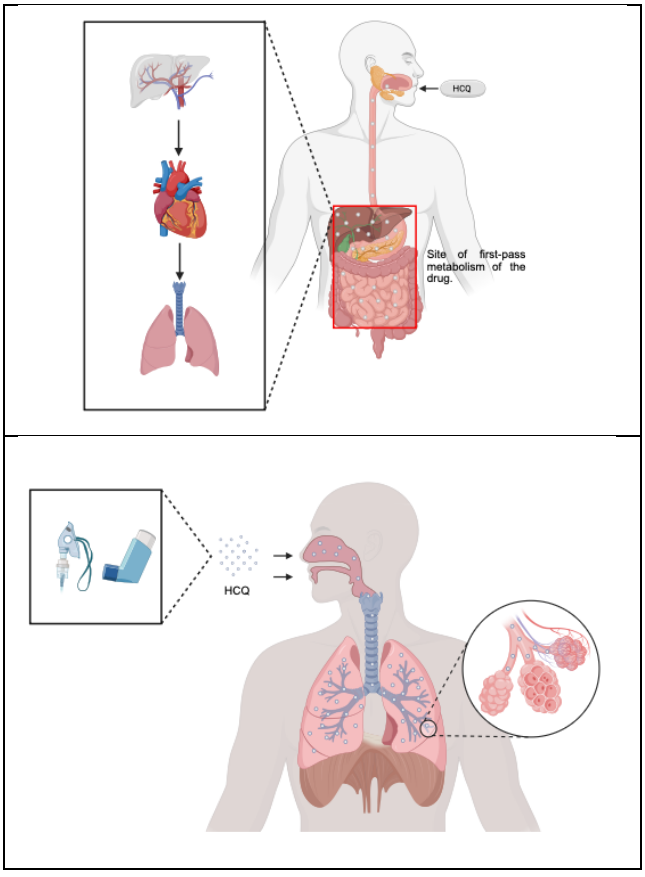

Illustration 1: Oral versus inhaled drug delivery.

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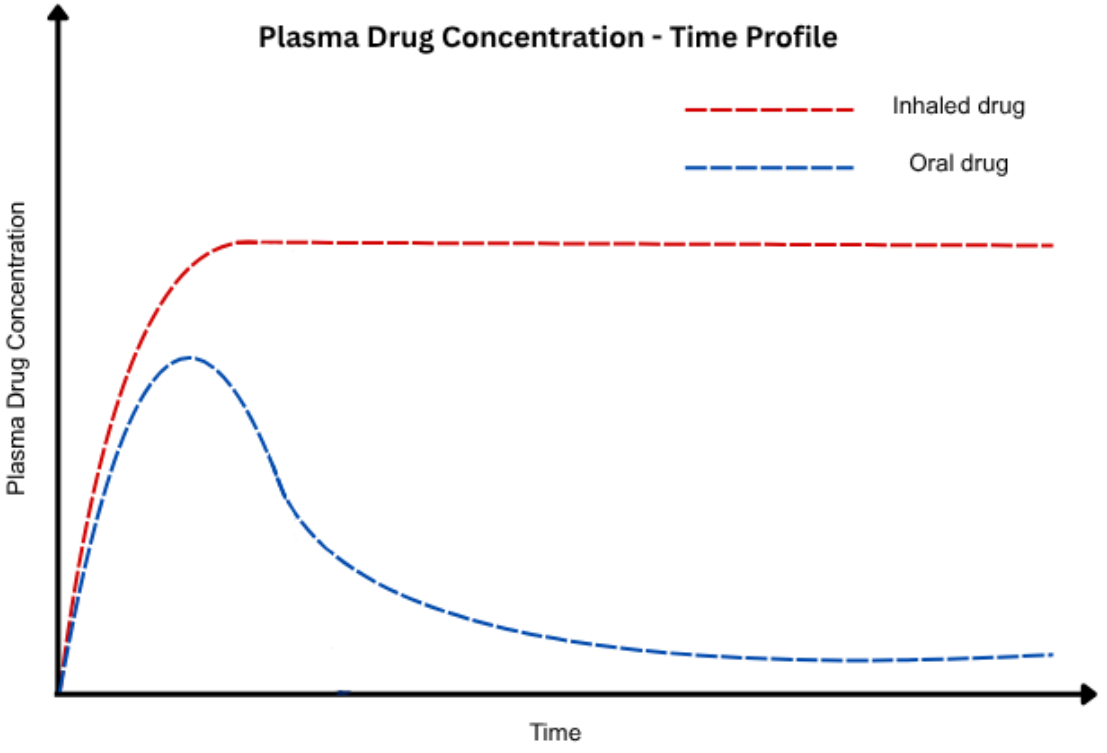

Figure 2: Pharmacokinetic rational for inhaled HCQ. (Blue) Oral administration results in significant systemic distribution and first-pass metabolism, leading to subtherapeutic of HCQ in lung concentration. (Red) Inhaled delivery of HCQ bypasses first-metabolism, allowing the drug to achieve high local concentrations in the lung while minimizing plasma levels.

A critical factor influencing the therapeutic effectiveness of HCQ is its lysosomotropic nature, a distinct feature that allows it to accumulate in acidic organelles, which is essential for its antiviral activity against SARS-CoV-2. As a diprotic weak base drug, HCQ presents in a non-ionized form at physiological pH, allowing it to permeate freely across membranes into endolysosomes and Golgi; once protonated, HCQ trapped within these acidic organelles (a process known as ion trapping), leading to concentrations several hundred-fold higher t (X. Chen & Geiger, 2020; Derendorf, 2020). This unique property of HCQ is essential for inhibiting SARS-CoV-2, as it raises the endosomal pH, thereby interfering with the pH-dependent viral fusion and uncoating processes (Bansal et al., 2021).

However, the effectiveness of this mechanism depends heavily on the specific pulmonary barriers encountered during the delivery of HCQ. The ability of HCQ to effectively penetrate these barriers and achieve sufficient concentrations in the lungs is crucial for its antiviral potential against SARS-CoV-2. Alveolar macrophages (AMs), the resident immune cells in epithelial cells of alveoli, represent both a primary barrier and a strategic target in this context (Hu & Christman, 2019). Although AMs are tasked with the swift elimination of inhaled micro- and nanoparticles through the mechanism of phagocytosis, their extensive lysosomal network designated them as the principal location for the sequestration of HCQ (Liu et al., 2023).

The conventional method of administration, like oral delivery, necessitates a significantly high systemic concentration to adequately fill these pulmonary 'lysosomal sinks,' which can lead to exceeding the threshold of cardiotoxicity prior to attaining therapeutic levels in the deeper regions of the lungs

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(Govender & Choonara, 2025). Conversely, local delivery via inhalation bypasses the systemic circulation, allowing for the direct saturation of alveolar macrophages and epithelial cells (Gao et al., 2025; Wang et al., 2024). This localized approach exploits the lysosomotropic properties of HCQ to establish a 'reservoir effect' within pulmonary tissues, thereby potentially prolonging antiviral efficacy while significantly mitigating systemic load and concomitant risks such as QTc interval prolongation.

Studies have proposed the use of HCQ aerosol for COVID-19 treatment (Kavanagh et al., 2020; Klimke et al., 2020). HCQ treatment on the infected patients via inhalation might improve the efficacy of the treatment, at the same time reduce the potential harms. In addition, Taher et al. (2021) suggested the use of polymeric pharmaceutical that easy to control and can be delivered specifically to the lung areas. To date, formulations that have been utilized on inhalable HCQ micro- or nano-particles for COVID-19 treatment are liposome (T. T. Tai et al., 2021), sodium alginate (Giridhar Reddy, 2021), nebulized solution (Idkaidek et al., 2021; Kolli, Semren, et al., 2022; W. Tai et al., 2021), and dry powder (O. Bentur et al., 2021; de Reus et al., 2022). T. T. Tai et al., (2021) conducted a study, investigating the pharmacokinetics (PKs) of liposomal HCQ and compared with the unformulated HCQ. Interestingly, compared to unformulated HCQ, liposomal HCQ showed higher (~30-fold) lung exposure, longer (~2.5-fold) half-life in lungs, at the same time showed lower systemic and cardiac exposure. Indeed, formulations contribute huge impact in determining the efficacy of drug delivery.

There is no restriction in approaching different mode of drug delivery systems; however, drug delivery via inhalation may provide a greater therapeutic efficacy for treatment targeting the lung region. An example can be taken from the use of cromolyn sodium for asthma management. Despite possessing excellent safety and tolerability, this drug is restricted for clinical application due to poor pharmacokinetic profile (Abd-Elaziz et al., 2020). Thus, compared to oral administration, this drug is more effective when, this drug is more effective when administered via inhalation (Abd-Elaziz et al., 2020; Fabbri et al., 1996; Minutello & Gupta, 2022). A contrast dissimilarity of the pharmacokinetic profile can be seen by HCQ since this drug is absorbed swiftly after oral administration (Fan et al., 2015; Furst, 1996) but it also has a long half-life (several weeks) and low systemic clearance (Fan et al., 2015; Perinel et al., 2020). Perinel et al. (2020) hypothesized, with justification, that the pathophysiology of SARS-CoV-2 infection may further affect the pharmacokinetics of the drug.

The dosage varies depending on the treatment indication. For autoimmune diseases, HCQ is often prescribed once or multiple doses range from 200 to 400 mg daily, whereas treatment for uncomplicated malaria requires 800 mg followed by 400 mg at 6 hours, 24 hours, and 48 hours after the initial dose (total 2000 mg) (Pastick et al., 2020). Based on Table 3, HCQ 400 mg daily via oral route was commonly prescribed for COVID-19 treatment in most studies. As for HCQ delivery via inhalation, the dosage varies among studies since most of the investigators were attempting to deliver lower inhalation dosage than oral prescription, directly to the lung, anticipating the delivered drug achieve maximum therapeutic effect, at the same time, minimize the systemic and other organs toxicity. The maximum safe dosage of 6.5 mg/kg/day was previously recommended by the 2009 Royal College of Ophthalmologists (RCO) and 2011 American Academy of Ophthalmology (AAO) before the AAO updated the maximum safe daily dosage to 5 mg/kg/day actual body weight (ABW) in 2016 (Jorge et al., 2018).

The major long-term adverse event associated with high daily dosage and extensive period of exposure of HCQ resulting a vision-threatening toxic retinopathy (Costedoat-Chalumeau et al., 2015; Jorge et al., 2018). However, in COVID-19 cases, the most concerning adverse effect relating to HCQ treatment is QTc prolongation as well as other cardiac abnormalities such as arrhythmias, and Torsades de Pointes (TdP). Based on Table 3, studies by Cavalcanti et al. (2020), Hernandez-Cardenas et al. (2021), Johnston et al. (2021) and Self et al. (2020a) reported QTc prolongation among SARS-CoV-2 infected patients when treated with HCQ, despite given and followed the maximum safe dosage per day guideline. Aside from that, The RECOVERY Collaborative Group (2020) reported a case of TdP that was deemed by the investigators to be related to HCQ. These could be attributed to the structural similarity of HCQ to class IA antiarrhythmic quinidine which blocks Na^+ and K^+ channels, resulting proarrhythmic effect by prolongation

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of QT interval, allowing TdP or ventricular arrhythmia to occur (Hooks et al., 2020; Villa Zapata et al., 2022; Yetkin et al., 2020).

On the other hand, a study on the administration of HCQ monotherapy via inhalation with dosages up to 20 mg on healthy volunteers showed that it is safe and the volunteers only experienced minor mild adverse effect that were not related to cardiovascular (de Reus et al., 2022). Another study by Hawari et al. (2023) reported the inhalation of HCQ among healthy participants were safe and tolerable as well as exerting a very minimal systemic exposure. A similar study with dosage up to 50 mg conducted by Bentur et al. (2023) also reported that the participants were mainly tolerate with the inhalation of the medication and experience mild graded severity of adverse events. However, they discovered a minimal change from the baseline on QT segments, with a maximum change of 34 msec, among healthy participants who received HCQ via inhalation.

The common mode of administration of oral HCQ for treatment not only for patients with malaria infection, SLE and rheumatoid arthritis but also applied for COVID-19 infected patients. However, delivering the drug via inhalation shall not be overlooked since it may provide a more targeted delivery to the lungs, potentially improving its therapeutic efficacy while reducing systemic side effects. This systematic review demonstrates no literature for inhalation of HCQ monotherapy on infected patients as the current available literatures and studies on inhaled HCQ monotherapy administrations on SARS-CoV-2 infected subjects are limited to preclinical settings. Exploring the potential of inhaled hydroxychloroquine delivery could be particularly beneficial for treating respiratory conditions like COVID-19, where the lungs are the primary site of infection and damage. Targeted lung delivery through inhalation may enhance the drug's ability to reach and act on the affected areas, while minimizing the systemic exposure and associated side effects observed with oral administration. This route of administration could offer a promising alternative to the current oral dosing regimens, potentially improving the therapeutic outcomes and reducing the risk of toxicity for patients.

CONCLUSION

This study compares the effectiveness of oral and inhaled HCQ in treating COVID-19. Across the 26 studies reviewed, oral HCQ was the preferred method due to clear prescription guidelines. However, oral administration often leads to insufficient concentrations in the lungs, affecting antiviral efficacy. Inhaled HCQ, on the other hand, promises higher therapeutic concentrations directly in the lungs with lower systemic toxicity. Despite the potential of inhaled HCQ for prolonged lung exposure, challenges like complex respiratory clearance mechanisms persist. While some studies reported favorable outcomes, such as reduced viral load and improved clinical status, others noted little impact on hospitalization rates or mortality. Both forms of HCQ treatment also showed adverse effects, such as cardiac abnormalities and gastrointestinal symptoms, warranting careful dosage optimization to prevent toxicity. Overall, while inhalation therapy may offer better lung-targeting for SARS-CoV-2, more clinical trials are needed to establish optimal dosing and confirm its efficacy.

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CONFLICT OF INTEREST STATEMENT

None of the authors had a conflict of interest.

AUTHORS' CONTRIBUTION

The authors' responsibilities were as follows —NSAZ, NAHM, and NEAR: designed the research and wrote the manuscript; KHJ, AFMR, SM, RY, MA, and YH: analyzed data; NAHM, MFMB, and ST: edited the manuscript; NSAZ: conducted the research and primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript.

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