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Pharmacotherapeutic and Computational Approaches for Biopharmaceutical Considerations towards Drug Development and Delivery against COVID-19

Payal Kesharwani [1,2], Deepika Deepika [3], Kanchan Bharti [4], Ankit Jain [5,*], Swapnil Sharma [1], Brahmeshwar Mishra [4], Vikas Kumar [3,6,*]

1 Department of Pharmacy, Banasthali Vidyapith University, Jaipur - 302001, Rajasthan, India
2 Rameesh Institute of Vocational Training and Education, Knowledge Park I, Greater Noida - 201310, Uttar Pradesh, India
3 Environmental Engineering Laboratory, Departmentd 'Enginyeria Quimica, University of Rovira i Virgili, Av. Països Catalans 26, 43007 Tarragona, Catalonia, Spain
4 Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi - 221005, Uttar Pradesh, India
5 Department of Materials Engineering, Indian Institute of Science, Bangalore, Karnataka, India - 5600126
6 IISPV, Hospital Universitari Sant Joan de Reus, Universitat Rovira I Virgili, Reus, Spain
* Correspondence: ankitjain@iisc.ac.in (A.J.); vikas.kumar@urv.cat (V.K);

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Abstract: The novel coronavirus disease (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affected millions of people worldwide at an alarming rate. Moreover, the development of vaccines is still hope, but its camouflage mutations during transmission are still a challenge. In the dire condition of this pandemic, drug repurposing with the exploitation of computational modeling has become the cynosure to repurpose the already existing drugs such as remdesivir, Favipiravir, dexamethasone, and other drugs at clinical levels. Furthermore, their safety and efficacy against COVID-19 remain a challenge in different age groups and populations with pre-existing conditions like heart disease, hepatic and renal impairment, pregnancy, and immunocompromised states. Moreover, computational modeling allows studying physiological and biochemical parameters on drug transport, delivery, and therapeutic efficacy of dosage forms. This review explicitly provides a comprehensive account of the challenges and opportunities for developing physiologically based pharmacokinetic models (PBPK) and pharmacodynamic(PD) models to establish a therapeutic dosage regimen based on dose selection, safety, and efficacy. We also highlight the pharmacologic targeting strategies for ACE receptors, toxicity concerns, combination therapy, and drug-drug interactions for different repurposed drugs against COVID-19. In dreadful scenarios, PBPK and PD models hold promise for human PK and dose prediction in COVID-19, along with paving new horizons to improve the therapeutic as well as immuno-therapeutic efficacy using nano-drug delivery approaches, computer-aided drug design (CADD), and speed up clinical trials with a better understanding of quantitative *in vitro* to *in vivo* extrapolation (QIVIE) and established PK data.

Keywords: Coronavirus 1; favipiravir; remdesivir; remdesivir; PBPK; PD models.

1. Introduction

The pandemic caused by a novel coronavirus (COVID-19), a respiratory disease, has caused worldwide social and economic disruption. Based on the current census of the total number of cases of COVID-19 (18.4 million worldwide to date) and the number of deaths

(6,92,000 worldwide to date)with a high global mortality rate of around 5% [1]. According to the public health advisory, older people and people with pre-existing medical conditions like diabetes, asthma, and cardiac disease are more susceptible to developing severe illnesses from this disease [2]. With the plethora of knowledge about the subdivision, protein structure, and virulence of this virus (SARS-CoV-2), many vaccines have also been developed for the treatment of COVID-19 [3]. Drugs have also given promising therapy such as remdesivir (RDV) and favipiravir (FVP). Recently, RDV has been given emergency use approval by the US FDA for critically ill patients [4]. Other therapeutic agents like hydroxychloroquine (HCQ), lopinavir/ritonavir (LPV/RTV), and ACE inhibitors are also under observation for their efficacy. Although some drug candidates can get approval for the treatment of COVID-19, their adverse effects after interacting with other co-medications cannot be kept at bay. As already discussed, the chances of mortality are higher in older and patients with comorbidities. Evidence has shown serious clinical implications in patients on immunosuppressive therapy when treated with HCQ and LPV/RTV initially followed by darunavir/cobicistat combination after being diagnosed with COVID-19 [5]. These complications demand an approach to monitoring the effective target drug concentration [6].

Efforts are ongoing to repurpose already existing marketed drugs for COVID-19 as they have known safety profiles[7]. But it is equally important to understand that the success of repurposing depends on the proper dosage regimen, efficacy, and principles of clinical pharmacology. Administering the correct dose needs knowledge about potency, protein binding, receptor affinity, and pharmacokinetic properties of the administered drugs[8]. Physiologically based pharmacokinetic (PBPK) model and pharmacodynamic models (PD) combine physiological properties, drug-specific properties, and an affinity for different active sites to model drug disposition and action for reducing viral load inside the human body [9]. Moreover, we should look at the setbacks of the number of clinical trials carried out on so many drugs for COVID-19 to find promising results (discussed later). Ideally, techniques like PBPK/PD modeling helps a lot in extrapolating the preclinical data to clinical settings, thereby decreasing the number of failures in clinical trials. Also, we all are witnesses of the time taken by the pharmaceutical companies to develop a drug against this disease in this global health emergency. However, this is unquestionable because a drug development process takes as long as 8-10 years, but currently, drug repurposing and PBPK/PD modeling can prove its worth in risk identification and cost reduction for designing effective treatment for this pandemic [10]. In this stage of finding a potential treatment for this disease, certain issues should be addressed to emerge an effective treatment. For instance, regarding the use of HCQ and RDV, is there any adverse effect of such drugs contributing to any other serious implication? Another issue is administering the correct dose to the right age group, and patients with accompanying illnesses since clinical trials are conducted with certain constraints of age and patients' health. Integrating preclinical data, clinical data, and PBPK/PD modeling can address the concern for the effective treatment of COVID-19.

Around 115 vaccine candidates are undergoing clinical or preclinical studies with approaches like nucleic acid-targeting, peptides, replicating and non-replicating viral vectors, recombinant proteins, and much more [11]. Still, no vaccine candidate has passed the clinical phase and been authorized for COVID-19. A collaborative effort is needed to develop an effective vaccine and drug along with computational modeling to fight against existing and future coronavirus infections. The outbreak's costly process involved in clinical drug development highlights the value of applying innovative approaches like drug repurposing,

pharmacokinetic/pharmacodynamic models, and artificial intelligence to facilitate efficacious and safe drug discovery. As no proven cure exists for COVID-19 until now, ayurvedic medicines have also been discovered. However, a large study is required to prove the efficacy of ayurvedic medicine against COVID-19.

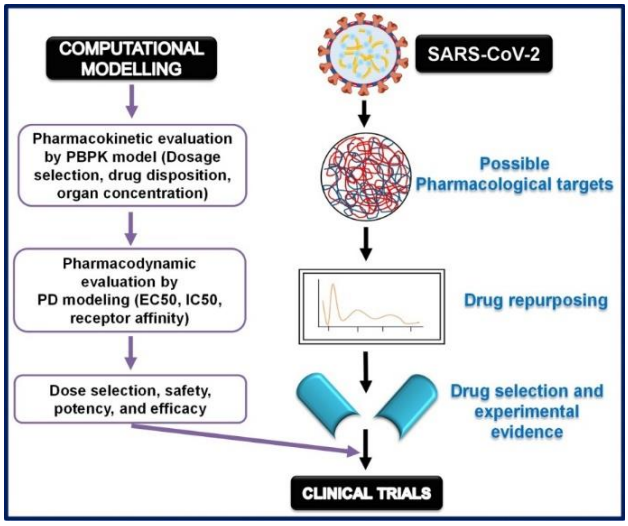

Figure 1. Overall pictorial representation of drug selection and computational modeling for improved treatment strategy for COVID-19[9-13].

This review aims to include the potential pharmacological targets for COVID-19 and toxicokinetic properties for treating COVID-19 patients with improved safety and potency of the drugs. This review will include summarized information about pharmacological therapy and the role of computational studies, especially the integrational PBPK/PD model for better efficacy, safety, and potency for treating COVID-19 patients across different age groups, giving an insight into the issues raised above (Figure 1).

2. Potential Pharmacological Targets and Associated Problems with the Therapy

In the wake of the COVID-19 pandemic, hydroxychloroquine was the first drug to gain attention for treatment, followed by recently approved remdesivir, favipravir. Apart from that, several other antiviral drugs, viz. ritonavir/lopinavir, arbidol, etc., came into the picture based on the *in vitro* and preclinical studies. Immune-based therapies have come out with relatively newer options for the treatment and have been entered into clinicaBishnoi l trials too. With the continuous use of these drugs, several concerns regarding the safety and toxicity of these drugs have been raised. The current discussion will mainly highlight the toxicities and drug-drug interaction of the current therapy, along with a brief description of their mechanism of action and the results of ongoing trials [14].

2.1. RNA-dependent RNA polymerase (RdRp) and protease inhibitors.

Based on the information that SARS-CoV-2 has protease (nsp3 and nsp5) and RNA-dependent RNA polymerase (RdRp, nsp12) as a part of their non-structural protein, many scientists have considered these two viral proteins as the most potential targets for COVID-19 [15]. The readers should understand the criticality of these enzymes in a viral lifecycle (Figure 2). With so many drugs proving effective against this ailment, RDV and FVP have received FDA approval [13]. RDV (GS-5734) is a broad-spectrum antiviral drug that is a prodrug and gets metabolized inside the cell to produce GS-441524. This GS-441524 gets phosphorylated

inside the cell and becomes polar; hence does not permeate outside the cell. It is converted into nucleoside triphosphate with the help of several kinases present inside the cell. The nucleoside triphosphate finally intervenes in the RdRp resulting in misintegrated viral RNA and hence the viral life cycle is ceased (Figure 2) [16].

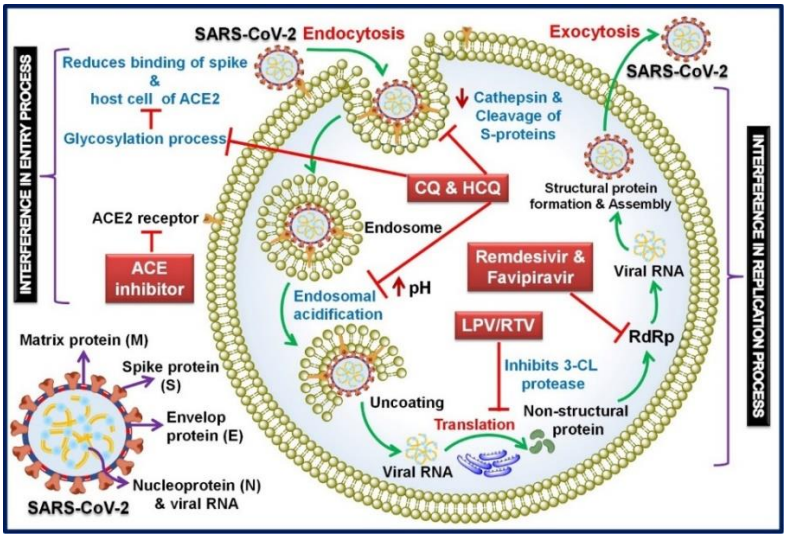

Figure 2. Potential pharmacological targets and mechanisms of action of different drugs for COVID-19 treatment [17-23].

According to a summary released by European Medicine Agency (EMA) by Gilead Sciences, Remdesivir is recommended for compassionate use for patients with high mortality risk and who require invasive mechanical ventilation. The molecule has received USFDA approval for the emergency treatment of COVID-19. No severe toxicity of Remdesivir with multiple-dose in monkeys has been revealed in the study. However, hepatotoxicity has not been denied [17]. Studies suggest that remdesivir effectively treats SARS-COV-2, which is demonstrated in an article where replication of SARS-COV-2 was inhibited in human lung cells and human airway epithelial cultures (EC50 = 0.01 μM). *In vivo* activity was tested by engineered chimeric SARS-CoV encoding on a viral target (mice). The viral lung load was seen to be diminished, and pulmonary function was boosted, suggesting the effectiveness of the method [22].

A capacious amount of research is going on with some immunosuppressive drugs, viz. dexamethasone, baricitinib, and tacilizumab, with RDV to be given as combination therapy for COVID-19. A broad-spectrum antiviral merimepodib is also being tested to be Shown to have a synergistic effect with RDV only at the early stages before the patient is transferred to mechanical ventilation. On the other hand, the use of baricitinib along with RDV is controversial in the early stage of infection as the former targets viral mechanisms and stimulates an immune response, but barcitinib is a JAK-inhibitor that may disable the patient's immune response against the virus at an early stage of infection. FVP is a prodrug with a purine nucleoside analog and an effective RdRp inhibitor, which gets ribosylated and phosphorylated intracellularly to form active metabolites FVP-5′-triphosphate (T-705-RTP). The active metabolite competes with the viral RdRp to terminate the viral life cycle. For safety and efficacy evaluation of this drug, various clinical trials conducted evidenced early viral clearance[24]. In an attempt to check the possible pharmacokinetic interactions of acetaminophen with FVP in vitro and in vivo, a study was done on hepatic S9 fraction and human volunteers, respectively. In the study, it was found that in vitro, it showed the decreased

formation of acetaminophen sulfate. However, in vivo, systemic availability of acetaminophen increased without any significant difference in Cmax. There was a hike in the area under the curve (AUC) of acetaminophen, limiting its dose to 3 g or less per day compared to 4 g per day when coadministered with FVP. However, this interaction showed no clinical implications making their coadministration safe [18]. There have been concerns about using FVP in patients with a history of gout, hyperuricemia, or kidney function impairment. LPV/RTV is a 3-CL protease inhibitor that has proven its efficacy against SARS-CoV, and MERS-CoV has been found effective against SARS-CoV-2 also despite the difference in the structure of HIV-protease and 3-CL protease [19].

The interactions can be supported by the computational kinetic and dynamic simulation to provide further confidence for safe and effective dosage regimens. The combination of lopinavir/ritonavir has been widely prescribed for HIV since 2006 [25]; there are several studies to show its interaction with other drugs. As of now, this combination is considered one of the probable cures for this ailment; there is scope to look for its propensity to interact with other drugs. Most of the interactions of LPV/RTV with other drugs are based on the fact that they fall into the protease inhibitors which are well known as inhibitors of the 3A4 isoenzyme of cytochrome P450 and P-glycoprotein. This becomes the key factor in the interaction of LPV/RTV with so many drugs in terms of increasing or decreasing their pharmacokinetic profiles depending upon the metabolic pathway of the coadministered drug. Fexofenadine [26] rosuvastatin [27], and buprenorphine [28] are a few examples of drugs whose Cmax and AUC are escalated several folds due to LPV/RTV where the inhibitory effect of RTV of CYP450 comes into play. Drugs such as phenytoin, which is predominantly a substrate of CYP2C9 and partially of CYP2C19, require therapeutic monitoring since LPV/RTV increases the clearance of phenytoin-inducing CYP2C9 [29].

The concern of interaction with other drugs also lies with RDV also, but this drug is still under investigation and has been permitted to use against COVID-19 in emergency conditions, only there has not been any significant study available to testify for its interaction with other drugs. With an extensive literature search with keywords like RDV and drug-drug interaction on Scopus and PubMed, no evidence was found explaining the interactions of RDV with other drugs. This further concerns the administration of RDV to severely affected patients in case they have to follow other dosage regimes for other diseases like diabetes, cardiac diseases, etc. The requirement of therapeutic drug monitoring comes into the picture in cases where not following the dosage regime could be life-threatening. In such scenarios, pharmacokinetic and pharmacodynamics modeling plays an important role in developing a suitable therapeutic dosage regimen. Looking at this situation, we can estimate that the mortality rate of COVID-19 is primarily because of pre-existing comorbidities.

2.2. Hydroxychloroquine and chloroquine.

HCQ and CQ picked up stream at a very early stage of this outbreak where their use had been justified based on their effectiveness against Zika virus and SARS-CoV. It was supported by its ability to inhibit the binding of a viral cell to the host cell's ACE-2 receptors, which are present in the lungs, heart, kidney, and intestine. HCQ and CQ are believed to interfere in ACE-2 glycosylation preventing the cell attachment to the ACE-2 receptor. A diagrammatic representation of the mechanism of HCQ and CQ is given in Figure 2. [30]. The emergency authorization led to another challenge of drug toxicity. This raises the need for an

integrative PBPK/PD model is required to design an effective therapeutic regimen amid the organ distribution and terminal half-life (50 days) of HCQ/CQ.

Previously published reports and clinical trial studies show significant drug-drug interactions prevailing with HCQ and CQ (Table 1). The clinical data reveals acute toxicity along with QTc prolongation with increased risk of torsade's de pointes [31]. CQ/HCQ is metabolized by CYP enzymes (CYP2C8, CYP3A4, CYP2D6, and CYP1A1).

Table 1. Drug-Drug Interactions and toxicity concerns with the treatment of COVID-19.

Drug(s)	Another Drug	Type of interaction	Toxicity	Ref.
CQ/HCQ	Ritonavir, lopinavir	Vacuolization of cardiac muscles	QT prolongation	[32]
	Tamoxifen	Inhibition of CYP2D6 enzyme	decreases the level of Tamoxifen	[33]
	Metoprolol	Inhibition of CYP2D6 enzyme	High concentration of metoprolol in plasma	[34]
	B blocker	QT prolongation	Cardiac arrhythmia	[35]
	Methotrexate	High concentration of metoprolol in plasma	effecting the liver	[34]
	Proton pump inhibitor: omeprazole	Affecting its oral bioavailability	change in gastric pH	[34]
	Metmorphin Azithromycin	Reduces insulin clearance Disturbs the myocardial electrical transmission	Hypoglycemia torsade's de pointes	[31,37]
Favipiravir	Acetominaphen	Increase in AUC	Clinically insignificant	[18]
	-	-	Increased level of blood uric acid	[19]
Lopinavir/Ritonavir	Fexofenadine	Increased Cmax and AUC	Increased plasma concentration can lead to potential toxicity*	[26]
	Rosuvastatin			[27]
	Buperonorphine		Liver toxicity	[28]
	Phenytoin	Increased clearance of phenytoin	Dose alterations are necessary for individual patient management	[29]
ACE-2 inhibitors	Ibuprofen	ACE 2 expression increases	Myocardial injury	[38]

Patients suffering from type II diabetes need special care and attention due to severe hypoglycemia observed in COVID-19 with reduced insulin clearance and increased pancreatic insulin release when given 400 mg/ day HCQ[39]. A patient deficient in glucose-6-phosphate dehydrogenase shows severe hemolytic anemia as a side effect when administered with HCQ and azithromycin[40] . The overdose of HCQ and CQ leads to central nervous system toxicity due to blockage of neuromuscular junction resulting in seizures and coma[13,41]. The overdose of HCQ also results in an anticoagulant effect [34].

The HCQ/CQ binds strongly with melanin pertaining to tissues in the eye and skin, leading to retinopathy and skin manifestation, respectively. This affinity produces a macular cone in the eye (outside of the fovea), decreasing lysosomes' phagocytic activity, and inducing epithelial atrophy in photoreceptor cells leading to retinopathy. There are many challenges that need to be overcome for prescribing HCQ and CQ for SARS-CoV-2. The CQ has high bioavailability (within 30 min in the blood); the formulation can be modified into a controlled release to make it targeted to the lung and show targeted release. The high dosing of the CQ can also be reduced to a minimum effective dose as its bioavailability is very high. Low dosing can also reduce toxicity through computational modeling. CYP2D6 is the primary enzyme that is responsible for the inactivation of CQ. The severe toxicity and harm related to treatment can be overcome by carefully selecting dose keeping and computation modeling considering the patient's clinical history.

2.3. ACE inhibitors.

Angiotensin-converting enzyme 2 (ACE-2) has been shown as a cellular entry receptor for viral entry inside the host body, indicating its role in the pathogenesis of COVID-19 [42]. A virus infectivity study was conducted by Zhou *et al*. on HeLa cells which demonstrated that COVID-19 might utilize ACE-2 as an entry receptor for entering ACE-2 expressing cells and not utilize other common receptors like dipeptidyl peptidase and aminopeptidase N [42]. Some reports by the scientific community suggest that ACE inhibitors may be useful, while others highlight on dangerous side effects of this therapy[43]. Data in humans are too limited to conclude, but until now, medical associations (European Medicine Agency, EMA) around the world have supported the use of ACE inhibitors for patients suffering from COVID-19 and hypertension, and other related morbidities.

ACE-2 is a homolog of angiotensin-converting enzyme I (ACE-1), widely expressed in the heart, kidney, and gastrointestinal systems. Recent data suggest expression in alveolar cells in the lungs, particularly AT2 alveolar epithelial cells [20]. ACE inhibitor drugs help maintain homeostasis of the RAAS system regulating blood pressure, water, and sodium balance around cells required for the proper functioning of tissues and nerves. Researchers at the University of California have initiated a clinical trial to investigate whether ACE inhibitors might be a cure for COVID-19. Around 560 participants have been recruited who are currently hospitalized or undergoing emergency treatment for COVID-19 in the United States [47]. But whether ACE inhibitors are potential agents in pharmacological therapy is a matter of debate and remains controversial among different medical communities and researchers.

Until now, no clear evidence shows the clinical trajectory towards the impact of ACE inhibitors in COVID-19 patients. A retrospective event from Wuhan, China, reflects poor outcomes such as hypertension, diabetes, and cerebrovascular disease as poor prognostic factors in patients with multiple comorbidities taking ACE inhibitor [46]. Acute myocardial injury is observed in a COVID-19 patient who already has cardiovascular disease due to an increase in the cellular expression of ACE-2 in the heart due to the intake of ACE inhibitors. If a hypertension patient discontinues ACE inhibitor in the case of SAR-CoV-2, blood pressure rises within 48 h. leading to hypertensive emergencies and subsequent acute pulmonary edema. The ACE inhibitors are neither recommended by WHO nor by FDA along with ibuprofen for symptomatic patients due to an increase in ACE-2 receptor expression [38] In general, healthcare providers encourage the usage of these drugs for young hospitalized populations suffering from SAR-CoV-2 without a history of any chronic disease [48]

2.4. Immunotherapy and other approaches

The pathological examination has indicated the immune hyper-activation and respiratory distress in severe COVID-19 patients suggesting the need for immune-based therapies like corticosteroids[49]. Corticosteroids like dexamethasone may modulate the immune response, especially interleukin-1 or interleukin-6 inhibitors. Being an anti-inflammatory may prevent or reduce the systemic inflammatory response developed in severe COVID-19 patients, thus preventing lung injury and organ system failures (WHO)[50]. Recently, RECOVERY, a multicentre randomized open-label trial, was conducted among hospitalized patients who showed a lower mortality rate in dexamethasone-administered patients and supplemental oxygen [51]. Corticosteroid therapy, when given in other novel coronavirus infections (MERS, SARS), resulted in delayed virus clearance Clinicians suggest that dexamethasone may lead to adverse effects in patients like hyperglycemia, secondary infections, and avascular necrosis. Being a moderate CYP3A4 inducer, dexamethasone may

decrease the efficacy of concomitant medications, especially CYP3A4 substrates[52]. Further studies need to be done to demonstrate the safety and efficacy of this drug. Other adjunctive treatments like human-derived products (convalescent plasma and immunoglobulin products), stem cell therapy, and monoclonal antibodies are proposed to have direct antiviral properties. Previously convalescent plasma has been used in infections like SARS, MERS, and Ebola. Currently, for COVID-19 clinical trials are ongoing to suggest the efficacy of such therapy [53]. Mesenchymal stem cells being anti-inflammatory, are also an effective option and has found to be effective in acute respiratory distress syndrome and influenza A H5N1-induced acute lung injury *in vivo* [49,54]. But, optimal dose, delivery route, and substantial variability are some of the reasons for the limited use of these stem cells. In such case scenarios, utilization of *in vitro*, *in vivo*, and epidemiological data along with computational modeling can be an effective option for designing a successful therapeutic regimen.

3. Computational Modelling

Drug repurposing through drug-target interaction, drug-drug interaction analysis, and computer-aided drug design (CADD) for identifying new molecular targets are fast computational approaches for identifying lead candidates against COVID-19 [23]. With efforts from the medical community and researchers, several targets have been screened through simple computational algorithms precisely against COVID-19[42]. Similarly, several drug candidates are proposed for treatment through drug repurposing and other computational techniques[23].

Apart from screening potential candidates, another big question arises about the potency and efficacy of these drugs in different population groups. For COVID-19, drug repurposing has been done to identify some potential candidates who showed efficacy in the *in vitro* and *in vivo* studies. Clinical trials have been initiated all around the globe to compare the efficacy of such therapeutic candidates as RDV, LPV, RTV, HCQ, and much more (discussed in the above section). Based on limited hints for efficacy and safety, RDV, HCQ, and other drugs have entered the clinical trial phase[55]. At this point, mathematical models like physiologically based pharmacokinetic models (PBPK), pharmacodynamic models (PD), quantitative in vitro to in vivo extrapolation (QIVIVE), and reverse dosimetry play an important role in simulating viral suppression profile, efficacy, and safety for a different population. It is important to consider the pharmacokinetic properties of drug candidates, which may impact dosing in the case of infected patients, pregnant females, children, the elderly, and those with other diseases. In such cases, underdosing or overdosing may occur for different population groups. The physiological differences among different age groups, especially the blood flow to various organs, enzymatic kinetics, and glomerular filtration, play an important role in developing an effective dosage regimen.

In the computational section below, the focus is on important factors for dosage selection and safety for different population groups using computational techniques. Further, other aspects such as drug-drug interactions, potency, and the role of protein binding of different drugs have been discussed.3.1. Dose selection within the therapeutic range.

The dosing regimen can be constructed for possible pharmacological targets to achieve adequate therapeutic concentration at the target site. Preclinical and some clinical information about pharmacokinetic (PK) properties of HCQ, RDV, LPV, and RTV exist in the literature, along with reported IC50 values[56]. If not, existing in vivo and in vitro data can be used for the PBPK model to assess the pharmacokinetic properties of drugs and concentration-time

profiles in different target organs. Well-constructed PBPK model plays a role in designing clinical studies by estimating drug PK profile and dosing scenarios [57]. Phase 1 PK data can be used as a benchmark, and further pharmacokinetics and other enzymatic changes can be incorporated into the model to validate and predict PK among the adult population. Also, the human PBPK model for HCQ and other antiviral drugs can also be simulated in different target organs such as the lungs, kidneys, and liver. For instance, Collin *et al*. published the PBPK model in the context of cancer-related autophagy for HCQ in mice and then adapted it in humans to simulate HCQ concentration in whole blood and urine across seven different doses[58].

The same approach can be applied to predict HCQ concentration for COVID-19 patients. In a recent article by Yao *et al*., the pharmacological action of HCQ and CQ was tested again for COVID-19 in the infected Vero cells in which HCQ (EC50=0.72µM) was more potent than CQ (EC50=5.47µM). PBPK was done for HCQ and CQ based on in vitro data, and the loading dose of 400 mg (bid) HCQ sulfate and maintenance dose of 200 mg (b.i.d.) for 4 days were simulated. The simulated dose for HCQ reached three times the potency of CQ phosphate when given 500 mg (b.i.d.) 5 days in advance [59]. The dosing regimen of CQ was used as a target for optimizing the HCQ dose[59]. In another article by Arnold *et al*., controversy has been raised on publication by Yao *et al*. on a dosing regimen for HCQ to get accurate efficacy and safety [55]. The author states that the partition coefficient (Kp) value used for calculating plasma concentration needs to be validated as the drug reaches distribution equilibrium in the target tissue in approx. 3 months in rats, and the high variability has been observed in reported values used by Yao *et al*. [55,59]. Such controversial debates give an opportunity to simulate the dosing scenario considering the possible errors and provide a window for improvement of the kinetic model.

Arnold *et al*. used the published HCQ Simcyp PBPK model to investigate the difference in HCQ concentration in lungs based on Kp values, determining HCQ conservative estimates lung concentration (5th percentile) compared to in vitro efficacy data and HCQ heart concentration for observing QT prolongation (Figure 3) [55]. Simulated value shows that loading dosing of 400 mg HCQ (BID*1day) followed by a maintenance regimen of 200 mg (BID*4 day) with a Kp lung value of 44, unbound HCQ levels did not reach the value used for clearing COVID-19 in vitro and levels were 5 fold higher than HCQ EC50. HCQ dosing regimen used in France (200 mgTID*10 days) gives unbound HCQ lung troughs which are required for clearing the virus *in vitro*. Unbound HCQ was used to calculate EC50 and the effective concentration needed to reduce viral load in the *in vitro* cells.

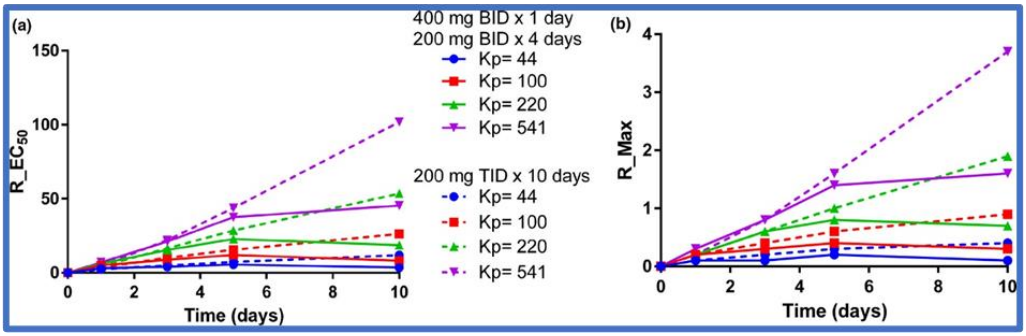

Figure 3. Simulated unbound HCQ lung concentration with *in vitro* efficacy data with varying partition coefficient values. Simulated concentrations used to calculate EC50 and concentrations needed to eliminate COVID-19 *in vitro* [Reprinted with permission, license number: 4878291436876] [55].

Additionally, this research result also demonstrates that for the simulation of tissue drug concentration, the data quality should be carefully considered by the researcher [55]. Cui *et al*. optimized the dosage regimen for CQ based on PBPK simulation considering distribution in different organs extrapolated from animal to human. A mechanistic PBPK model was developed, taking into account the active transport of CQ, and accumulation of CQ inside cells. It was validated with 38 concentration-time profile studies from a different populations.

Table 2. Pharmacological targets used for SARS-COV-2.

Pharmacological category	Drug	Target	Mechanism of action in the treatment of SARS-COV-2	Ref.
Antivirals	Atazanavir, danoprevir, darunavir	SARS-CoV-2 Mpro	Inhibit the viral replication and also averts the release of cytokine storm-associated mediators.	
	Remdesivir	interferes with the nsp12 polymerase	Inhibits the replication of SARS-CoV by producing a cleavage product of viral polyproteins.	[63]
	Favipiravir, galidesivir	RdRp of RNA viruses	Blocking SARS-CoV-2 replication	[64][65]
	Lopinavir/ritonavir	3CLpro and PL2pro proteases	Blocking SARS-CoV-2 replication	
	Daclatasvir	N-terminus of NS5A	HCV NS5A replication complex inhibitor, which affects both 101 viral RNA replication and virion assembly	[66]
Antimalarials	Artemisinin/artesunate	spike protein	Endocytosis inhibition mechanism, anti-inflammatory	[67]
	Atovaquone	viral RdRp or 3C-like protease	Inhibit SARS-CoV-2	[68]
	Chloroquine, hydroxychloroquine	ACE-2 receptors	They increase the pH of acidic cellular organelles, counteracting virus replication	[69]
Immunosuppressants	Cyclosporine	Calcium-dependent interleukin (IL)-2 production.	Block viral replication. It blocks the calcineurin activity by complexing with cyclophilin in the cell and suppresses gene transcription of IL-2	[70]
	Sirolimus	Block viral protein expression	Inhibit the release of virion	[68]
	Tacrolimus	-	Inhibited SARS-CoV-2 replication	[68]
Antibacterials	Doxycycline	Cytokines	Reduce pro-inflammatory cytokines levels and chelate matrix metalloproteinases used for cell fusion and viral replication	[65]
Antidiabetic drugs	Dapagliflozin	-	Reduce lactate levels, reduces oxygen consumption in tissues	
Kinase inhibitors	Baricitinib	AP2-associated protein AAK1	Reducing SARS-CoV-2 endocytosis	[72]
NSAIDs	Acetylsalicylic acid		Inhibit virus replication and platelet aggregation and show the anti-inflammatory effect	[73]

The widely validated model developed based on active transport inside cells gives confidence and is highly helpful for predicting the right dose in the population. However, further validation is needed considering disease-related pathophysiology[74]. In translating the dose from the adult to the pediatric population, allometric scaling with PBPK is required to predict the correct dose and plan pediatric clinical trials [75]. However, the accuracy of allometric scaling has been demonstrated by many small molecular drugs for children. However, still, in some cases, empirical adjustment for ontogeny and maturation is needed,

especially for smaller age groups [75]. The PBPK model needs to consider such adjustments while scaling at different age groups.

A study by Laurens *et al*. simulated the dose of CQ based on allometry by PBPK for children of different age groups. Simulation by the PBPK model shows that drug exposure varies if a similar body weight dose is administered to children of different ages and adults. Different cumulative doses have been proposed for different age groups, 35 mg/kg for 0-1 years, 47 mg/kg for 1-6 years, 55 mg/kg for 6 months-12 years, and 44 mg/kg for adults of CQ[36]. Different dosing scenario for various age groups which the PBPK model has supported has been provided in Table 2. As we know that limited treatment exists for COVID-19, it is highly important that the COVID-19 dose regimen be constructed using computational modeling to achieve therapeutic concentration at an effective site [8].

3.2. Safety.

WHO and other medical associations currently rely on drug repurposing as these drugs have a good and established safety profile[76]. As some of the drugs are being administered to patients with COVID-19 based on drug repurposing, which poses a threat to safety for infants, children, and other health compromised patients[77]. For instance, CQ is used for malaria in all age groups. A few medical associations recommended the same antimalarial dose for treating COVID-19-infected pediatric patients. It raises the obvious question are these doses safe enough and efficacious to treat COVID-19 in different age groups? The pediatric population likely needs a lower dose per kg of body weight, especially when the drug is getting metabolized in the liver and partially excreted through the kidney. As all the organs are immature at the time of birth, there exists the need to go for redosing in the case of neonates and infants [36]. Both the European Medical Association and US Food and Drug Agency support using the PBPK model for determining the dose that is safe for different age groups [8,36].' Ciu *et al*. demonstrated that they altered liver metabolic enzyme activity and renal flow to estimate safety from CQ among special populations. They did not find any drastic increase in exposure in renal or hepatic impaired patients, senior, and pregnant women. Still, they consider that in the case of a sensitive population like pediatrics, impaired patients, CQ exposure can increase dramatically, causing safety concerns.

Further application of the PBPK model includes safety profiling for specific population groups and adjusting the therapeutic regimen for COVID-19 patients. Homolok and Kodvanj proposed the pharmacodynamic model of CQ and other lysosomotropic drugs on which such a model can be applied to assess their safety[78]. Pharmacodynamic models can be integrated with pharmacokinetics to observe the dose receptor activity relationship for COVID-19 patients. Such a model will allow investigation of active moiety's safety, dosing, and efficacy. Until now, there are few published models on active moieties considered for COVID-19 for establishing safety among different population groups. For future studies, different population groups and the physiology of diseased patients should be considered to simulate therapeutically effective doses.

Key findings suggest that the coadministration of multiple drug classes leads to complications in the safety of specific drugs. Drug-drug interaction (DDI) holds the utmost importance in the COVID-19 scenario, where most admitted patients suffer from existing diseases leading to increased risk. In such a scenario, the quantitative PBPK and pharmacodynamic model for DDI play a significant role in understanding PK interaction, elimination, and accumulation of active moiety inside the human body [33,79]. However, for

studying COVID-19 and other drug interactions, the PBPK/PD model has not been used extensively, but there lies a scope for using these models for such studies. In past inhibitory potential, metabolic inhibitions, and agonistic effects were assessed using the PBPK model combining the coadministration of two different drugs. For instance, Min *et al*. have shown that the PBPK model has been extensively used for drug-drug interaction to simulate CYP450-mediated DDI and transporter-mediated DDI along with genetic polymorphism and special population[80]. Gracia *et al*. developed a mechanistic PBPK model for itraconazole and its two metabolites using different dosing regimens, formulations, and DDI studies with midazolam. The model predicted DDI between midazolam and itraconazole with a 2-fold error [81]. Similarly, the PBPK model for considering DDI can be developed using in vitro or in vivo data. A recent study by Jafari *et al*. has shown that anticancer patients suffering from COVID-19 are at higher risk of such interactions considering renal and hepatic impairment background due to chemotherapy[33]. This highlights the need for an integrative PBPK/PD model for simulating a safe and effective dosage regimen in case of multiple medications.

3.3. Potency and protein binding affinity.

Little information has been published about the potency of the repurposed drugs, and most of this information is related to the antiviral activity of these drugs on other viruses. Some pharmacodynamic models have been published for COVID-19. But mostly considering EC_{50} or IC_{50}, EC_{90} should also be considered for designing an effective and potent dosage regimen. This information can be utilized while simulating an effective dose through the PBPK and PD model. Goncavales *et al*. used a target cell limited model with an eclipse phase for simulation dynamics of COVID-19 viral load with data from 13 hospitalized patients in Singapore. They simulated the time course for starting viral treatment and the efficacious level needed for reducing viral load. The impact of treatment on peak viral load was inversely correlated with treatment initiation time. Antiviral efficacy was calculated based on the compounds' pharmacokinetic and pharmacodynamic properties, around 66% for LPV/RTV and 33% for HCQ[82]. The author states that at these levels, drugs may not dramatically affect peak viral loads if they are administered after symptom onset. Such a case scenario and utilization of PK/PD properties emphasize the need for PK/PD model simulation to administer a loading dose followed by a maintenance dose for maximizing the efficacy of COVID-19 drugs. One of the important parameters affecting the drug's systemic disposition at the target site is plasma protein binding, represented by the fraction unbound in plasma. Mainly free drugs bind to the target site and are available at the action site as plasma bind drugs become inaccessible[83]. This parameter must be considered as some drugs like LPV demonstrate a high binding affinity for simulating an effective dosage regimen again COVID-19. The integrated population pharmacokinetic model was developed for LPV to investigate the action of alpha-1 acid glycoprotein and the effect of unbound and total LPV on viral dynamic and efficacy parameters. Wang *et al*. have calculated the virion clearance rate. Through the HIV-1 dynamic model, viral load trajectory was calculated, demonstrating the efficacy of the treatment regimen for LPV/RTV through PK/PD modeling and simulation[84].

Another study by Cremades *et al*. developed an integrated PBPK/PD model for demonstrating the safety and efficacy of high-dose HCQ. The author simulated that 400 mg b.id and 600 mg b.i.d. have shown lower viral load, and 800 mg b.i.d. may result in QTc prolongation (Figure 4) [86]. This study suggests that such a modeling and simulation approach

is highly beneficial for COVID-19 to determine therapeutically significant target drug exposure and safe dose, which should be achieved for durable therapeutic success. It emphasizes integrative modeling considering the mechanistic pharmacokinetics and pharmacodynamics modeling with preclinical and clinical data to validate the results. Such kind of integrative modeling will be highly helpful in fast, effective, and low-cost drug development for the treatment of COVID-19 patients.

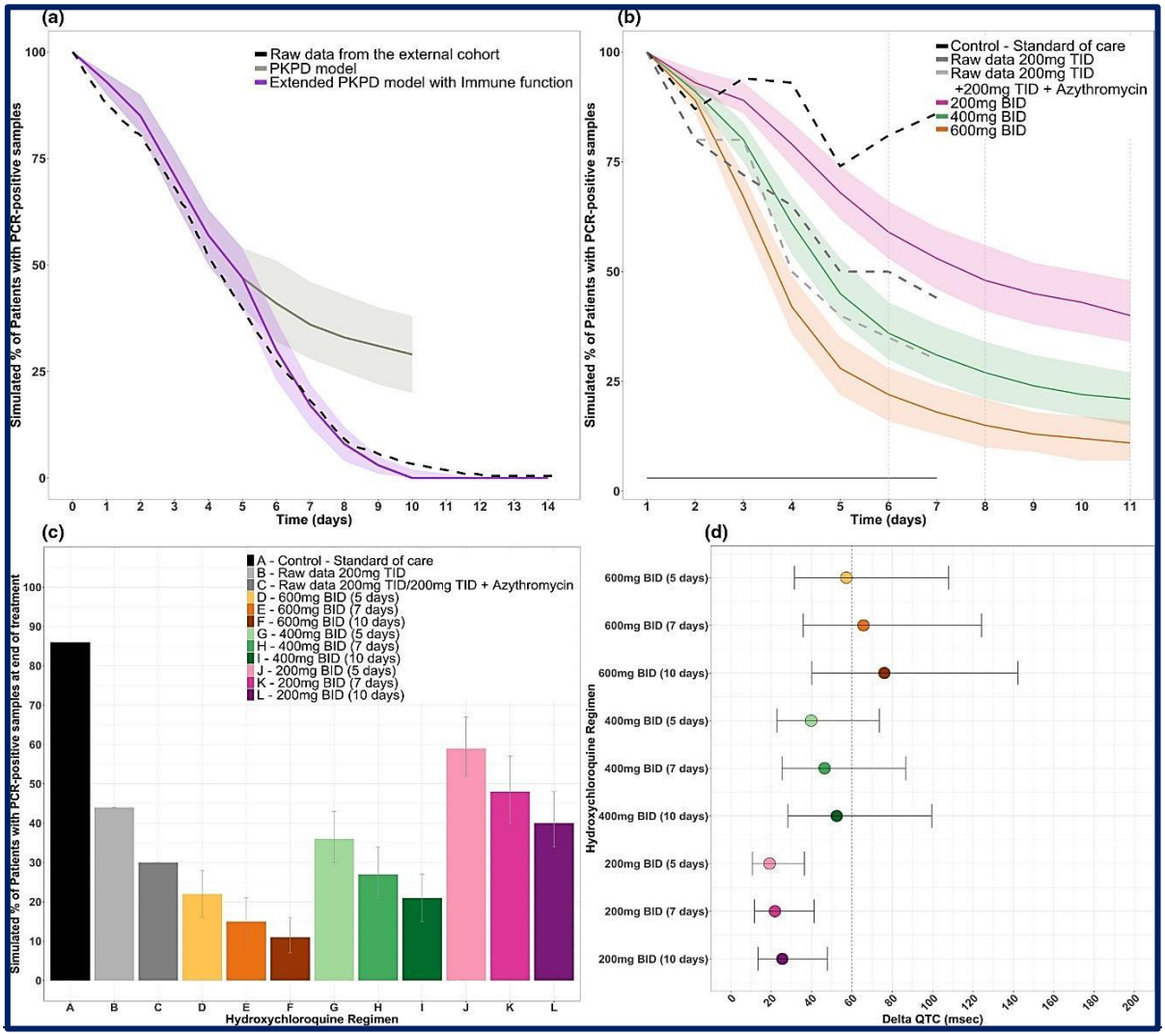

Figure 4. Simulation study for efficacy and safety of HCQ with different dosage regimens through PKPD showing predicted longitudinal viral load, immune effects through simulation, and further simulation for optimal dose range [Reprinted with permission, license number: 4878291436876] [85].

3.4. Computational modeling and drug delivery.

PBPK/PD model also finds its application in nanoparticle-mediated drug delivery especially focusing on the targeted approach. This section focuses on modeling and simulation for targeted drug delivery, providing the base for developing such a model to treat COVID-19. In the case of COVID-19, a computational model for the drug delivery approach has not been developed yet, but there is a scope for such models. For instance, Harashima *et al*. developed an integrated PK/PD model for free and liposomal doxorubicin formulation to simulate the conditions for drug carriers to obtain maximum efficacy for peritoneal tumors [87]. In the pharmacokinetic model, free and bound doxorubicin disposition was simulated based on the release of active moiety from the formulation in the circulation and tumor compartment. The cell-kill kinetic pharmacodynamic model represented a number of tumor cells with a free

concentration of doxorubicin in the target compartment. The validity of the model was tested in a rodent model. In another article by Ribeiro *et al*., for the drug therapy of p53 and cell cycle regulation, a framework was developed for a mechanistic integrated PK/PD model for dynamic tumor chemotherapy[88]. The proposed model is a representation of drug therapy, including molecular and macroscopic aspects of cancer. Similarly, targeted drug delivery for the treatment of COVID-19 can be simulated for the prediction of a drug at active sites. Additionally, conceptual compartments can be created for simulating drug release from the formulation and integrated into the model with emphasis on physiological processes and can be used to design safe and effective therapy.

The menace of diseases like COVID-19 can be curbed either by a vaccine or an effective therapy with a suitable drug delivery that controls the viral infection rapidly, as this is an acute condition. In the current landscape, where we have almost surpassed the level of drug discovery in the form of drugs like RDV and FVP along with other effective drugs, there is a hardcore requirement for a carrier system that compliments the therapeutic efficacy of the drug toward curing the disease. Nano drug delivery system can furnish us with the platform as in this case, the size of the article is scaled down to nanometer range there is an avenue for the chemical, physical and optical changes in the material characteristics[14]. As we have already discussed, the disease is acute, and we are mostly concerned with patients having comorbidities. Terminating the disease at its earliest stage or any prophylactic measure can be helpful. Shuai Xia and coworkers worked on the same approach by understanding the molecular mechanism that triggers the virus fusion of viral cells with host cells.

According to the study, the S2 subunit of the spike protein of SARS-CoV-2 has heptad repeat 1 and heptad repeat 2, which interacts to form a 6-helical bundle that mediates the fusion of virus-cell and host cell membrane. Hence, they prepared the EK1 peptide series to prevent cell-cell fusion and found EK1C4 highly effective in limiting membrane fusion. This study is not limited to control of SARS-CoV-2 only rather, and it has applicability for SARS, MERS, and other human coronaviruses too. The envisaged intranasal formulation of the EK1C4 can be promising in decreasing the viral load in human lungs[60]. A lot has been discussed about the role of silver, copper, and zinc incorporated nanomaterials in controlling fomite-mediated infections [89].

However, the current review focuses on the role of nanomaterials to be given as a carrier system for the drugs available for the therapy of disease. Interestingly a study reports the efficacy of nano-silver colloids owing to the antiviral properties of silver nanoparticles and the delivery of the required antiviral inhibitory concentration. It is to be taken through inhalation by anyone who identifies any early signs of the infection[61]. The concern of potential toxicities caused by the drugs being used can be solved by alternative drug delivery systems and routes of administration, where a nasal route is proving very promising. Even after so many studies on the toxicity of HCQ, the scientific community suggests using aerosol formulations to reduce the early-stage symptoms and the QT prolongation happening with the oral route of administration. There are certain conditions like consideration of an alternate route of administration, a lower dose of HCQ from 800 mg daily to a scaled-down dose (2-4 mg b.i.d. by inhalation) according to the weight of lungs with respect to whole-body [88] There are several reasons which are in accordance with RDV to be administered as nebulizer inhalation in combination with IV administration 90. Due to poor hepatic stability, RDV will likely result in complete first-pass metabolism; there is no scope for it to be given orally [17].

Also, it is far-fetched that the desired tissue penetration and distribution will occur in the human lungs through IV administration, which is the most affected organ in COVID-19. This statement has been supported by the study done on monkeys, where the lung concentration of nucleoside triphosphate was found to be negligible after 10mg/Kg IV dose [90]. Sawittree Sahakijpijarn *et al*. have even suggested thin-film freezing as an efficient method for preparing powder for inhalation [91]. Similarly, in the case of FVP though it comes as a tablet formulation alternate route of administration with more targeted drug delivery systems should be explored. In conformity with previous research, Lammers et al. have suggested nano-formulating the drug and its administration through IV or intranasal route. This approach seems promising since studies have proved dexamethasone nanomedicine effective in autoimmune diseases, wound healing, and cancer [92].

There is abundant literature available for lung targeting of drugs by using nanocrystals[93], polymeric nanoparticles [94], solid lipid nanoparticles [95], and other drug delivery systems. These delivery systems have utter requirements of controlled parameters like particle size, the geometry of particles, and surface charge [96]. The challenges every drug delivery system suffers are always the limiting factors in converting that system into a final formulation that patients could take with good compliance. Nevertheless, these factors do not stop the research and development of advanced drug delivery systems. It's the need of the hour that even over time, we find an effective vaccine for the disease, and the trials on developing newer and more efficient drug delivery systems should be carried on.

Nano-drug delivery systems have emerged as a novel theranostic and diagnostic tool based on specific targeting for the treatment of COVID-19[97]. The nano-drug delivery approaches will act as a powerful tool for repurposing drugs, which will help improve COVID-19 therapeutic management.

A nano carrier-based drug delivery system can overcome the various problems related to solubility and low bioavailability by adopting different approaches such as modifying its pharmacokinetics/pharmacodynamics properties resulting in dose reduction of a drug, improved toxicity, and virus suppression. The nanocarrier is found to be similar in size and shape to SARS-CoV-2, which enhances the attachment to spike protein, thus resulting in the localized killing of the virus[98]. They also protect RNAi, nAbs, protein, peptides, and other biologicals from premature drug release and degradation and help in dodging renal and hepatic clearance[99]. The nanocarriers such as dendrimers, liposomes, carbon nanotubes, polymeric nanoparticles, nanostructured lipid carriers, etc. can be used as a medium that will direct to a specific site or epitopes containing SAR-CoV-2 by attaching with antibodies, carbohydrates, peptides, or protein. The nanomaterials (acid functionalized multi-walled carbon nanotube) can cause the viral receptor blockage, preventing the attachment and entry to the ACE 2 receptor. This can be used as an approach to killing the SAR-CoV-2 virus[100]. Also, nanocarriers have the ability to cross the biological barrier and are effective in the reserve sites[101]. As discussed above and observed in COVID-19 cases, patients are suffering from significant toxicities, so adequately designed targeting approaches and computational modeling will help reduce such effects. Understanding drug toxicity and adopting a suitable Nano strategy would maximize its application in finding an appropriate treatment for the SARS-CoV-2 virus.

Researchers are working on the development of multipronged drug nanocarriers, which show programmed drug release [102], high therapeutic potential [103], high drug loading, biocompatibility, and targeted delivery with reduced side-effects [104]. Scientists at the University of Paris-Sud in France are working on virally induced hyper-inflammation (cause

of the increase in mortality in case of COVID-19). The uncontrolled pro-inflammatory states cannot be reduced until targeted. Therefore, a prodrug-based nanocarrier was developed by conjugating squalene with adenosine encapsulating α tocopherol, a natural antioxidant (SQAd/VitE) [105]. In mice models with acute inflammation, they succeeded in improving bioavailability, high drug loading, and targeted delivery to the inflammatory site when tested in a model of acute inflammatory injury. The nasal method of injection and emulsifying drug delivery system is also being studied by researchers to treat COVID-19. The intranasal drug delivery system can provide effective and safe management of virus with the benefit of the mucosal membrane since most infectious pathogen begins their infectious cycle at the mucosal surface. The mucosal membranes extend the residence and release time of the drug with quick absorption ensuring the drug delivery to the target site [97]. These drug delivery strategies can be beneficial in finding a suitable treatment for COVID-19 [106]. The computational modeling and experimental approach will be useful in designing the drug delivery system with the help of emerging nanocarriers for selective localization of drug(s) to affected lung tissues. It will not only improves the efficacy of the drug but also mitigate the toxicity concerns to vital organs [9,107].

4. Conclusions and Future Perspectives

COVID-19 represents the global pandemic challenge of this generation, and the scientific community all over the world is making painstaking efforts to develop effective nanotherapeutics through computational and experimental studies for repurposing the old (effective) drugs by exploring combination drug-drug/gene therapy, including nanocarrier based approaches. However, safety and efficacy being of prime importance is the biggest hurdle to achieving effective treatment. The combination therapeutic approach is turning out to be safe and effective in reducing the viral shedding of COVID-19. It can minimize the risk of antiviral resistance, untoward toxicity, and high/multiple dosing in monotherapy and dramatically alleviate symptoms. The University of Hong Kong has recently demonstrated promising results for the Covid-19 treatment with a combination of HIV medicine lopinavir-ritonavir, hepatitis drug ribavirin, and multiple sclerosis therapy interferon β 1-b[108]. This triple combination showed promising results in lessening symptoms and curbing viral shedding and hospitalization time.

Different countries are in a race to find the possible treatment for COVID-19 indulging them in various clinical trials. Some studies are undergoing clinical trials, but many have not shown promising results. The failure of clinical trials can be considered due to the small size of the group selected for the study. Also, the severe side effects shown by the drugs increase the mortality rate and duration of stay in the hospital. The first clinical trial conducted in China for RDV failed due to severe side effects [109]. One of the studies published in The Lancet says that the HCQ has been found to increase the mortality rate in the hospital due to severe side effects such as arrhythmia or irregular heartbeat [110-112].

This review thus emphasized toxicity concerns and computational approaches to expedite drug development and industrial scale-up of screened molecules to overcome threatening COVID-19 comorbidities and mortalities. Scientists are looking at a multipronged strategy to fight this battle, as vaccine development is still an aspiration in the near future because of aberrant mutations in the viral genome. Increased clinical trials and preclinical studies ongoing to investigate potential therapy for COVID-19 promise a large amount of pharmacokinetics and pharmacodynamic data. Such data can be utilized to design the COVID-

19 targeted dosing regimen to address the challenges of effective concentration at the target site and opportunities against SARS-CoV-2.

Moreover, computer modeling can also be beneficial for monitoring target drug concentration by estimating the pharmacokinetic profile of drug(s) in the presence of other co-medications. The integration of clinical pharmacology and the PBPK/PD modeling can hold promises for bringing new horizons to maximize the chances of developing a successful therapeutic regimen with a better trade-off in economic and time-honored aspects for treating this pandemic.

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Conflicts of Interest

The authors declare no conflict of interest.

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