Repurposed drug against COVID-19: nanomedicine as an approach for finding new hope in old medicines

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Abstract

The coronavirus disease 2019 (COVID-19) has become a threat to global public health. It is caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) and has triggered over 17 lakh causalities worldwide. Regrettably, no drug or vaccine has been validated for the treatment of COVID-19 and standard treatment for COVID-19 is currently unavailable. Most of the therapeutics moieties which were originally intended for the other disease are now being evaluated for the potential to be effective against COVID-19 (re-purpose). Nanomedicine has emerged as one of the most promising technologies in the field of drug delivery with the potential to deal with various diseases efficiently. It has addressed the limitations of traditional repurposed antiviral drugs including solubility and toxicity. It has also imparted enhanced potency and selectivity to antivirals towards viral cells. This review emphasizes the scope of repositioning of traditional therapeutic approaches, in addition to the fruitfulness of nanomedicine against COVID-19.

1. Introduction

COVID-19 (coronavirus disease 2019) is a potentially life-threatening disease mainly affecting the respiratory system [1]. It was first identified in Wuhan city of China in December 2019 [2]. The etiology of COVID-19 includes severe acute respiratory syndrome and most infected persons experience mild to moderate respiratory illness [3]. It is very widely reported that the lungs as the main organ particularly involved in this disease, while few literatures have reported involvement in other organs as well including the liver and kidneys [4]. Ultimately, it can impair the metabolism and excretion of the drugs taken to treat the disease. Furthermore, the body’s immune system overreacts to the severe form of COVID-19 infection and release inflammatory mediators (like cytokines) into the bloodstream which can damage multiple organs including the heart under the influence of a phenomenon called ‘cytokine storm’ [5].

However, patients who are immunocompromised or suffer from chronic degenerative diseases like diabetes or cardiovascular problems are more prone to serious illness [6]. It is observed that the transmission of disease occurs through the transfer of high viral loads in the upper respiratory tract via droplets of saliva or discharge from the respiratory tract of infected persons. Individuals can also shed and transmit the virus while being asymptomatic [7].

COVID-19 has disseminated throughout the world, emerged as a global pandemic, lashing major events to be postponed, and forcing many people into quarantine and self-inflicted isolation. As of 9th April 2021, about 28,94,295 people died so far from the COVID-19 outbreak and there are 13,35,52,774 confirmed cases in 223 countries and territories [8]. The rate of fatality is still under review [8]. Health agencies and governments are attempting to brush the curve off, alleviating the spread through society and social awareness while the scientific
community, researcher, academician, and people from the pharma industry turn their attention to gain insight into the genetic makeup of coronavirus and its mode of infection for better understanding of efficient treatment possibilities [9].

The pandemic COVID-19 has a relatively low mortality rate but the high rate of contamination or R0. Consequently, the number of deaths is increasing day by day, and with the second wave surging in cases is unstoppable. This has resulted in saturation of the hospital infrastructure and a sudden dip in the world economy. The whole world is engaged in efforts to discover efficient methods of treatment for COVID-19. Some old drugs (Re-purposed drugs) have shown efficacy against this disease in recently conducted clinical trials [10]. Despite that, several promising drugs failed as a potential treatment for COVID-19 in the clinic because of the undue side effects or lack of efficacy. Nanomedicine based drug delivery approach offers promising strategies to conquer the constrain of conventional therapeutics by offering a platform with enhanced efficacy and specific targeting strategies to gain the anticipated benefit [11–14].

This review presents an account of existing medications with potential efficacy against COVID-19. The in-vitro and in-vivo efficacy, potential toxicity, and adverse reaction of these drugs are discussed with all due consideration of their feasibility against COVID-19. The critical role of nanomedicine as an approach for finding new hope re-purposed drugs is also presented in the manuscript.

2. Therapy for COVID-19 management

Medicine that combat COVID-19, treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), protect the lives of chronically ill patients, save healthcare staff and those at high risk of infection are yet to be identified. Under the current situation, the medical team can only provide symptomatic treatment and supportive care which include oxygen and ventilator support depending upon the appearance of the symptoms. Common symptoms associated with COVID-19 are illustrated in figure 1. An array of different treatment options with some older drugs have been proposed with favorable outcomes [15–19]. SARS-CoV-2 is a + sense, single-stranded RNA encapsulated β-coronavirus [20]. It replicates with the help of non-structural protein (such as 3-chymotrypsin-like protease, papain-like protease, and RNA-dependent RNA polymerase) and structural protein (spike glycoprotein). SARS-CoV-2 infects the cells through the viral structural spike (S) glycoprotein by binding to angiotensin-converting enzyme2 (ACE2) receptors and host type 2 transmembrane serine protease (TMPRSS2) [21] (illustrated in figure 2). The non-structural proteins (such as 3-chymotrypsin-like protease, papain-like protease, and RNA-dependent RNA polymerase) and ACE2 receptors are recognized as a key point to target the SARS-CoV [20, 21]. Besides, some additional drug targets include immune modulators [21] at the viral entry point as shown in figure 2. Table 1 summarizes the physicochemical and physiological characteristics of the different repurposed drugs having potential in COVID-19 management.

![Figure 1](image_url)
2.1. Therapy with antiviral drugs

2.1.1. Remdesivir

Remdesivir is an investigational broad-spectrum, potent antiviral drug [19, 37]. It is an adenosine analogue and known to block the viral infection by inhibiting the viral RNA-dependent RNA polymerase (RdRp) and cause premature termination of RNA transcription [19, 27, 37]. Its efficacy was demonstrated against paramyxoviridae, filoviridae, and novel coronaviruses in different in-vitro and in-vivo studies [25]. A preclinical study in an animal model has demonstrated significant activity of remdesivir against COVID-19 and high resistance to the genetic barrier [19]. Also, it has been administered to several patients with a positive test for COVID-19 infections to study its efficacy in the USA, Europe, and Japan [38]. A clinical trial is currently underway to assess the effectiveness and safety profile of remdesivir against patients suffering from COVID-19 [21, 38]. The reported side effect of remdesivir in three patients (a total of 12) includes gastrointestinal disturbance with rectal bleeding and elevated aminotransferase [39]. A clinical study of remdesivir against the Ebola virus reported that patients experienced hypotension and finally died due to cardiac arrest [40].

2.1.2. Ribavirin

It is a guanine analogue that works by inhibiting the viral RNA-dependent RNA polymerase (RdRp). Its effectiveness against other coronavirus makes it a therapeutic option for COVID-19, demanding high-dose, and combination therapy [21]. Previous studies suggest that it may induce severe dose-dependent hematologic toxicity, resulting in hemolytic anemia and transaminase elevation [29]. Another clinical study found that about 40% of the patients receiving ribavirin and interferon may require blood transfusion [41]. Also, it is a well-reported teratogen and has to be avoided during pregnancy [21, 30]. In conclusion, safety data of ribavirin from
| Drugs                      | Molecular weight (g/mol) | Solubility                                      | LogP | Adult dose | Target / Mode of action                                           | Side-effect / Adverse reaction                                      | Precaution                                                                 | References                     |
|---------------------------|--------------------------|-------------------------------------------------|------|------------|------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------|
| Chloroquine phosphate     | 319.9                    | Very slightly soluble in water; soluble in dilute acids, chloroform, ether | 4.63 | 500 mg p.o every 12–24 h for 5–10 days.                          | –Glycosylation of host receptor.- Endosomal alkalization.- Inhibition of PICALM. | –Nausea, vomiting, abdominal cramps.-QT prolongation.                | –Dose adjustment in renal impairment.-May be used in pregnancy if the benefit to risk ratio is high | [21–24]                      |
| Hydroxychloroquine sulphate | 335.9                   | Water solubility (0.0261 mg ml⁻¹)               | 3.87 | 400 mg p.o b.i.d. for 24 h, then 200 mg p.o b.d for 5 days.     | –Same as Chloroquine phosphate                                    | –Gastrointestinal disturbance.-Retinopathy in high dose             | –Use with caution in renal impairment and hepatic impairment.-May be used in pregnancy if benefit to risk ratio is high | [21–24]                      |
| Remdesivir                | 602.6                    | Water solubility (0.339 mg ml⁻¹)                | 2.2  | 200 mg i.v. infusion o.d. followed by 100 mg i.v. infusion o.d. for 5–10 days | –RNA polymerase inhibitors                                       | –Elevated reversible transaminase-Kidney injury                     | –Not much sufficient data available.-Better to avoid in pregnancy        | [21, 25–27]                   |
| Ribavirin                 | 484.14                   | Water solubility (33.2 mg ml⁻¹)                 | −1.9 | Dose vary based on the indication                               | –RNA polymerase inhibitors                                       | –Common gastrointestinal disturbance.-Dose-dependent hematologic toxicity.-Birth defects or death in an unborn baby | Dose adjustment in Renal: CrCl 30–50 ml min⁻¹ 50% reduction CrCl <30 ml min⁻¹ 75% Reduction. Contraindicated in pregnancy. | [25, 28–30]                   |
| Favipiravir               | 157.104                  | Water solubility (8.7 mg ml⁻¹)                  | 0.49 | -Dose vary based on the indication                               | –RNA polymerase inhibitors                                       | –Elevated reversible transaminase-Common gastrointestinal disturbance | –Contraindicated in pregnancy and lactating women.                      | [21, 31]                      |
| Lopinavir/Ritonavir       | 720.946                  | Water solubility (0.00192 mg ml⁻¹)              | 3.91 | 400 mg/100mg p.o. b.i.d for up to 2 weeks                       | –Inhibits 3 chymotrypsin-like protease.                          | –Gastrointestinal disturbance-Pancreatitis, hepatotoxicity          | –Cautiously use in case of hepatic impairment.                           | [21, 32–34]                   |
| Arbidol (Umifenovir)      | 477.4145                 | Water solubility (0.00678 mg ml⁻¹)              | 4.97 | Target S protein/ACE2 membrane fusion inhibitors 200 mg p.o t.i.d for 1–2 week | –Elevated reversible transaminase-Common gastrointestinal disturbance | –Cautiously use in case of hepatic impairment.                       | –Cautiously use in case of hepatic impairment.                           | [21, 35, 36]                   |
its use against other coronaviruses and its considerable toxicity suggests its limited significance for the treatment of COVID-19.

2.1.3. Favipiravir
It is a prodrug of favipiravir ribofuranosyl-5'-triphosphate (a purine nucleotide) [21]. The active moiety of favipiravir inhibits RdRp and terminates premature viral replication. Most of the favipiravir’s animal data are obtained from its antiviral activity against influenza and the Ebola virus. Limited clinical studies have been reported in support of its clinical application against COVID-19 [21].

2.1.4. Other antiviral drugs

2.1.4.1. Lopinavir/ritonavir
It is an FDA-approved combination of drugs for oral administration against HIV [21, 34] which inhibits 3-chymotrypsin-like protease [21, 34]. There is limited published data available for the effectiveness of lopinavir/ritonavir against COVID-19. However, some case reports and small retrospective, non-randomized cohort studies are available for use in COVID-19. The most frequently administrated and investigated dose of lopinavir/ritonavir in the case of COVID-19 is 400 mg/100 b.d for 2 weeks [21, 32].

2.1.4.2. Arbidol (umifenovir)
It is a promising refocused antiviral drug acting on S protein/ACE2 interaction which prevents fusion of the viral envelope to the membrane [42]. Its use is approved in Russia and China as prophylaxis against influenza and respiratory viral infections [21, 25, 43], and currently under investigation for use in COVID-19.

2.2. Therapy with chloroquine and hydroxychloroquine
Chloroquine phosphate (CHQ) and hydroxychloroquine sulphate (HCHQ) are oral prescription medicines against malaria and certain inflammatory conditions (like rheumatoid arthritis and lupus erythematosus). Based on the report published by Vincent et al (2005) [44], the pharmaceutical scientists have proposed that CHQ and HCHQ may succeed in treating the case of COVID-19. The investigation reported that CHQ was effective in the prevention of coronavirus from spreading in pre-treated as well as post-treated coronavirus-infected cell cultures [21, 34]. The potent antiviral and anti-inflammatory effect of CHQ account for its dynamic potency against COVID-19. It hampers the replication of the virus in different ways. Many viruses, including COVID-19, utilize the acidic environment of endosomes within the cell membrane to breach and release the genetic material for replication [23, 45] (figure 3). CHQ enters into the endosomal compartment, enhances the compartment pH due to its chemical structure, and renders the compartments alkaline [45] (illustrated in figure 3). The increase in compartment pH results in blockage of the replication process by the CHQ [45]. Vincent et al (2005) reported that CHQ prevents coronavirus from plugging into angiotensin-converting enzyme-2 (ACE-2) receptors and ultimately affecting viral replication [44]. Following the promising in-vitro results, more than 20 clinical trials have been started in various hospitals in China. The findings obtained from >100 patients exhibited the superiority of CHQ compared to the control group about minimizing the pneumonia exacerbation, length of symptoms, and latency of viral clearance [15, 23, 46]. The first successful clinical trials by the Chinese team recommended the administration of 500 mg of CHQ b.i.d in patients infected with COVID-19 [23]. This has contributed to the inclusion of CHQ in the prevention and treatment guidelines for COVID-19 pneumonia in China [15, 23, 46].

Further, a promising derivative of CHQ, HCHQ is under review in clinical trials for the prophylaxis of COVID-19 infection. Till now, no clinical guidance is available on the therapeutic use of HCHQ against COVID-19. However, based on in-vitro activity against COVID-19 and its greater availability worldwide compared to CHQ, HCHQ has been used in COVID-19 patients [23, 47]. Furthermore, the results of an open-label non-randomized clinical trial demonstrated that HCHQ alone or in combination with azithromycin can significantly reduce the viral load in specimen samples of upper respiratory tracts [9]. However, QT prolongation associated with HCHQ and azithromycin requires precaution for its use in patients with chronic diseases such as renal impairment and hepatic disorders.

2.2.1. Chloroquine and hydroxychloroquine against COVID-19: understanding the mechanism from nanomedicines
Successful treatment of any disease includes the ability to resolve the issues like poor drug delivery, fast elimination, drug resistance, and acceptability of patients [13, 48]. Consequently, highly efficient drugs with on-site delivery approaches are urgently needed [13]. To resolve these issues, various strategies have been developed, some have been approved for enhanced site-specific drug delivery and, in certain instances, to improve the safety and efficacy of therapy [13, 48]. Nanomedicine based drug delivery system provides an approach to achieve the
Objective of therapy by improving the safety and efficacy of medicine [12–14]. Despite the promising potential of nanomedicine, significant obstacles persist in its success. For example, more than 90% of intravenously administrated nanomedicine are primarily taken up by Kupffer cells of the hepatic tissue [13, 48, 49]. The use of CHQ has been one of the forward-looking perspectives to address such an issue associated with nanomedicine [50].

Over the years, CHQ has also proved its potential to disrupt the biological processes in higher animals that could be utilized for cancer treatment [48, 51, 52]. CHQ, for instance, prohibits cell autophagy by obstructing the last steps of this phase, which then makes cancer cells more susceptible to drug-induced programmed cell death [48, 51, 52]. CHQ also induces tumor vasculature normalization, which improves the delivery of drugs [48, 51–53]. More recently, CHQ has been shown to significantly decrease the commutation of nanoparticles (NPs) in the hepatic tissue by influencing macrophage activity [48, 50, 54]. It acts as an inhibitor of autophagy. It is a poor diprotic base that is di-protonated and stuck in lysosomes, increasing the pH of the lysosome [55]. The corresponding rise in pH precludes the ultimate step of the autophagic pathway which ultimately results in the formation of autophagic vesicles in the cytoplasm, preventing the output and reprocessing of vital nutrients/metabolites that leads to cell damage and consequently cell death [55, 56]. Also, CHQ has been approved as a potential contender that reflects the Kupffer cells’ ability of NP internalization, without affecting cellular internalization of NP within the cancerous cell [48, 50]). A suggested mechanism for CHQ assisted restraint of cellular uptake of NPs by macrophages is the inhibition of protein phosphatidylinositol-binding clathrin assembly (PICALM) [48, 50, 54, 57]. PICALM depletion has recently been reported to suppress clathrin-mediated endocytosis and found to be a prevailing route for the internalization of fabricated nanomedicine [54, 58]. Molecular studies have demonstrated that CHQ restricts the expression of PICALM [54, 57]. PICALM is a pod-selecting clathrin port that triggers and drives the curvature of the membrane and in doing so governs the rate of endocytosis [54, 58]. Furthermore, chloroquine is reported to deter lysosomal acidification and thus avoid fusion with endocytic vesicles [54, 59]. Deterring lysosome fusion is possibly to have issues with upstream

Figure 3. Underlying mechanism of action of CHQ and HCHQ against COVID-19. It inhibits viral binding to its cell surface receptor by suppressing the PICALM and prevent the biosynthesis of sialic acid along with inhibition of pH dependent endocytosis.
endocytic trafficking, resulting in a 'traffic jam' paradigm that prevents the successful cargo transport from and to the cell membrane [57]. Another pathway involved in the suppression of clathrin-dependent endocytosis is illustrated in figure 3.

2.2.2. Toxicity and adverse reaction
CHQ and HCHQ are mainly excreted by the liver and kidney [60]. Therefore, its excretion decreases in patients suffering from hepatic or kidney dysfunction, pushing them at higher risk of toxicity due to over-drug accumulation [60]. Some of the adverse effects are categorized as non-severe and may not affect the continuation of therapy while others are severe and require discontinuation of the medication [60]. Gastrointestinal (GI) disturbance and skin disorders are examples of few non-severe adverse events while retinal, neuromuscular, and cardiac toxicity categorized are severe adverse events associated with the use of CHQ and HCHQ. The symptoms of GI disturbance may include weight loss, stomach pain, diarrhea, loss of appetite, nausea, and vomiting [60–62], while the manifestation of dermatological disorders includes skin irritation, scratching, hair damage, exfoliative dermatitis, erythoderma, urticaria, and eczematous eruptions [60–62]. Also, CHQ and HCHQ may induce irreversible toxicity such as retinopathy which is an example of one of the most severe dose-dependent adverse reactions [60, 63]. Patients undergoing treatment with CHQ and its derivatives need periodical screening to exclude the chances of progress in retinopathy. Additionally, regular follow-up is also required to assess the chances of any other risk factors. Cardiac risk is usually rare in patients on CHQ and HCHQ therapy but may be life-threatening in the chances of occurrence [60]. Congestive heart failure, conductive disorders, and cardiomyopathy in combination with hypertrophy have been reported and discontinuation of therapy is often inadequate to preclude toxicity [60, 64]. Furthermore, CHQ and HCHQ therapy have also been associated with chances of QT interval prolongation, T wave inversion, ST-segment depression, sick sinus syndrome, and malignant ventricular arrhythmias [60, 64]. Besides this, neuromuscular myopathy caused due to CHQ and HCHQ therapy typically involves proximal muscles and may be linked to cardiac myotoxicity as well. Caucasoid origin and associated renal insufficiency are major contributing factors responsible for its manifestation [60, 65–68].

3. Targeted therapy as an approach in management of COVID-19: drug targeting to lungs

In coronavirus infections, the binding and entry site of the virus is the angiotensin-converting enzyme 2 (ACE2) receptor, which is an enzyme attached to the cell membranes of cells located in the lungs, arteries, heart, kidney, and intestines [69–71]. On the other hand, ACE-2 lowers blood pressure by catalyzing the hydrolysis of angiotensin II (a vasoconstrictor peptide) into angiotensin a vasodilator [72]. It has a protective effect against virus-induced lung injury after infection. So, blocking and/or decreasing the attachment of the virus to receptors in pulmonary host cells could help in the fight against infections as well as in the production of antibodies against ACE2.

The benefit of using the repurposed drugs are, that they have been used harmlessly in the past and the information about their optimal dose and pharmacokinetics is also known. Some of these drugs are already proven to be effective in vitro against a broad range of viruses [23], but these findings are inconclusive because of the disappearance of SARS and the studies are neither clear nor fully explained [73]. It is very difficult to find any drug in this time of emergency of COVID-19, especially the ones having a better safety profile than these repurposed drugs. The costs of these repurposed drugs are also economical [74, 75]. Hence, these drugs are the ultimate alternatives for prophylactic/curative treatment in people who are exposed to this novel coronavirus. If the clinical data of these repurposed drugs is confirmed with biological results then these drugs will be the simplest approach to treat and prevent COVID-19 [76].

The virus that causes COVID-19 enters into the humans through the droplets of cough and sneezes of an infected person and reaches into the respiratory tract [77, 78]. The human respiratory tract is divided into two regions, the upper regions which contain the nasal cavity, sinuses, nasopharynx, oropharynx, larynx, and trachea and bronchioles, alveolar ducts and alveolar sacs forms the lower region [79]. The symptoms of COVID-19 in healthy persons start to appear when the virus infects the lower region after infecting the upper region [80]. The functions of the complex structures of lungs are to provide the barrier to prevent the entry of environmental pollutants and microorganisms [81].

Pulmonary drug delivery occurs when the drug-loaded in dosage forms collides with the liquid which lines the surface of the lungs epithelium [82, 83]. The deposition mechanisms of the drug in the lungs depend on the aerodynamics of the particles of the dosage forms [84, 85]. The deep penetration of dosage forms inside the lungs depends on the aerodynamic diameter of a particle [84, 86]. The regular functions of respiration such as air humidification, temperature control in the thoracic and tracheobronchial regions, and gas exchange in the alveolar interstitial region pose challenges for drug delivery to the lungs [87]. Delivery of drugs through the
upper region of the pulmonary area have limitations due to smaller area of delivery, lower blood flow, presence of mucus layer (which traps inhaled substances), and filtration of foreign objects [88]. The ciliated cells have a large surface area and direct connection to the systemic circulation in the lower region of the lungs, making them an ideal site for pulmonary drug delivery. The branched nature of alveolar macrophages and pulmonary surfactant (phospholipids, proteins, and mucus) decreases delivery efficiencies [89] with mucociliary and cough clearance mechanisms of lower regions of the pulmonary area being the other possible challenges in drug delivery through this region.

The delivery of nanomedicine-based dosage forms with their specific attributes can be used to overcome these challenges [90]. It has been reported in previous researches that the microparticles (MPs) with aerodynamic sizes between 1 and 5 μm could escape the mucociliary clearance and deposit in the lower airways [91]. The delivery of nanomedicines through the pulmonary route can enhance and maintain local drug concentration for the treatment of the disease [92]. If the delivery of the drug will be limited to the effective site, the dose required for the treatment and adverse effects can also be possibly minimized [93]. While the delivery of these repurposed drugs is mainly from an oral route, which causes variability in bioavailability due to gastric conditions [94]. After recognition of ACE2 receptors in coronavirus infection [95], the nanoformulations can be designed to specifically interact and bind with this receptor. If some natural or artificial ligands or target-specific antibodies are attached with the nanoformulations, then the delivery of dosage forms can be made to specific receptors (targeting) [96, 97]. Targeting can be passive if the loading of drug or formulation in the receptor is due to its biophysical properties [98]. The targeting can be active if done using an active process such as electroporation [99], sonoporation [100], and magnetic targeting [98] of a repurposed drug for delivery to the specific ACE2 receptors.

4. Scope of nanomedicines in management of COVID-19

The major challenges related to viral infections such as SARS-COV (Severe Acute Respiratory Syndrome), 2003; MERS (Middle East respiratory syndrome), 2012 and COVID-19 is that we don’t have any effective drug for the treatment. Therefore, treating the COVID-19 infections with the repurposed drugs is more effective than with newer drugs after viral infections. The development of a newer vaccine typically takes a long time and several rounds of protocols and trials. However, inadequate cellular internalization of the repurposed antiviral drug is one of the major limitations for the effective treatment of COVID-19. Also, limited aqueous solubility and bioavailability, reduced biological potential, high risk to benefit ratio, and greater toxicity limit their use [101, 102]. These restrictions open up new opportunities for emerging strategies to improve the efficacy of repurposed drugs and facilitate their cellular uptake. To overcome these limitations, several nanomedicine-based platforms have been developed to increase the therapeutic effectiveness of repurposed antiviral drugs [103]. Nanomedicine-based antiviral therapeutics offer multiple opportunities to address the shortcoming of conventional antiviral therapy [104]. Some underlying challenges such as low aqueous solubility, poor bioavailability [11, 13, 90, 105, 106] can be resolved by the concept of nanomedicine, by altering the pharmacokinetics and pharmacodynamics properties of drugs that may result in reduced dose, toxicity reduction, and enhanced drug bioavailability and finally the suppression of viral spread [97, 102, 107]. Also, nanomedicine can bypass the biological barrier and achieve therapeutic concentration in viral reservoir sites [97, 108]. Nanomedicine with inherent controlled/sustained release properties is one of the best solutions to reduce the risk effect of patients’ compliance and rebound of the virus during the treatment period [104]. Thus, the nanocarriers strategy is a potential tool to be utilized for drug repurposing and to improve the therapeutic outcome in COVID-19 [97, 109]. Furthermore, nanocarriers possess salient features of being smaller in size, having large surface area, high drug loading efficiency coupled with sustained drug release profile, and improved overall performance of the loaded therapeutics in such novel drug delivery system (NDDS) [11, 13, 90, 105, 106].

The advantage of nanotechnology in medicine is due to its distinctive physicochemical characteristics of nano size, shape, hydrophilic or hydrophobic nature, and possible conjugation of ligands on its surface [11–14, 90, 110]. These physicochemical attributes of nano dimension give better functionality, sensitivity, efficiency, and specificity in their therapeutic applications [110]. The various nanoparticulate system utilized to encapsulate different therapeutics may differ from each other based on their chemical composition. Different type of nanoparticulate system can be classified into those made from biodegradable materials (such as chitosan, dextran, phospholipids, and poly(lactic-co-glycolic acid), etc), carbon-based materials (such as graphene and nanotubes), metallic nanoparticles (which contain oxides and sulfides of metals), and semiconductor nanoparticles (such as quantum dots) [111]. The biopharmaceutical performance and utilization of these nanoparticulate systems for various biomedical applications are significantly influenced in a biological system by their particular chemical composition (such as polymeric, lipidic, metallic, and inorganic nature) along with
other structural features which include physical characteristics (such as size, shape, and stiffness), surface characteristics (such as surface charge and hydrophobicity), and surface functionalization with particular functional groups and targeting ligand [112]. These characteristics can make nanomedicine an attractive tool in COVID-19 management for the treatment.

Figure 4 illustrates the underlying mechanism in the pathogenesis of COVID-19 and the potential benefits of repurposed drug encapsulated nanoparticulate system as a nanomedicine in management of COVID-19.

Patra et al., have written a comprehensive discussion on the different type of nanoparticle system utilized to improve the overall safety and efficacy of various therapeutics and summarized characteristic features of the different clinically approved nanomedicine (such as doxorubicin-loaded liposomes as Doxil®/Caelyx™, sirolimus nanocrystals as Rapamune®, albumin-bound paclitaxel nanoparticles as Abraxane®, and estradiol micelles as Estrasorb™, etc) available in the market [111]. Also, recently Delshadi et al have written a comprehensive discussion on the various nanoparticles utilized to improve the overall safety and efficacy of particularly antiviral agents [113].

The advantages and disadvantages of different types of nanoparticulate systems exploited for therapeutic applications are illustrated in figure 5. Furthermore, toxicity apprehension related to the different nanoparticulate systems (particularly nanoparticulate systems of inorganic nature) utilized for the therapeutic/diagnostic applications is a major concern. The particle size, shape, and surface charge are likely to contribute to cytotoxicity [114]. The smaller size of nanoparticles has a larger specific surface area and which makes them interact with different cellular components (like nucleic acids, proteins, fatty acids, and carbohydrates) of the living system. The higher cellular uptake of the smaller particles correlated with higher toxicity depending upon the nature of nanomaterials [115]. In general, the nanoparticulate system tends to deposit within different types of cells, including macrophage-type cells (both histiocytes and blood phagocytic cells) and RES (Reticuloendothelial system) cells in the body, and commonly induce DNA damage and oxidative damage particularly in the case of a nanoparticulate system of inorganic nature [116]. The different groups of nanomedicine that have the potential to be repurposed to be used in treatment for COVID-19 are discussed below. Table 2 summarizes the outcome of nanomedicine as an approach to improve the biopharmaceutical performance of different repurposed drugs having potential in COVID-19 management.
4.1. Lipid-based nanomedicines
Numerous lipids have been investigated as a carrier for antiviral drugs \[135, 136\]. The prodigious advantage provided by lipid nanocarriers includes enhanced drug stability, inert, and controlled drug release profile making them suitable candidates for nanoformulation \[136, 137\]. Furthermore, targeted drug delivery, the biocompatible, biodegradable, and physiological nature of lipids promote their safe use \[136\].

Lipid-based nanoformulation includes liposome, solid lipid nanoparticles (SLN), nanostructured lipid carrier (NLC), nanoemulsion (NE), and nanoemulsion preconcentrate as self-nanoemulsifying drug delivery system (SNEDDS).

4.1.1. Liposome
Liposomes are phospholipid bilayer, colloidal vesicles with a center aqueous core. They are capable to entrap and carry both hydrophilic and lipophilic drugs simultaneously \[11, 12, 90, 105\]. It may be surface conjugated with various ligands for site-specific targeting \[11, 12, 90, 105\]. In the research commenced by Patel \textit{et al} (2017), proliposomal formulation of lopinavir was developed which showed remarkable improved oral bioavailability. Bioavailability study in Wistar rat demonstrated that developed formulation exhibit 2.24- and 1.16-fold higher bioavailability than pure drug and available marketed formulation respectively \[117\]. Recently, Maniyar \textit{et al} (2019; 2019) reported the formulation and evaluation of lopinavir-loaded spray-dried liposomal cream for topical application. The cream showed superior drug deposition as well as drug release \[118, 119\]. The histopathological study demonstrated the inertness of cream and \textit{in-vivo} bioavailability studies showed the many-fold increase in bioavailability of lopinavir \[118, 119\]. Ahammed \textit{et al} (2017) demonstrated the development and \textit{in-vivo} evaluation of biotin functionalized ritonavir proliposomes for lymphatic targeting by lipid thin-film hydration method \[120\].

4.1.2. Solid lipid nanoparticles
Solid lipid nanoparticles (SLNs) are nanometric colloidal systems comprising of solid-lipid matrix stabilized by surfactant in aqueous media of around 10–1000 nm in size \[109, 138, 139\]. SLNs are designed to achieve sustained-release profile, enhanced drug stability, improved drug loading, and site-specific targetability because of being able to be functionalized \[109, 138\]. Furthermore, SLNs offer the advantage of enhanced permeability and bioavailability, reduced Pgp efflux, decreased first pass and cytochrome P-450 metabolism, and improved uptake by the lymphatic system \[109, 140\]. In a study conducted by Negi \textit{et al} (2015) glyceryl behenate-based SLNs of lopinavir were developed to enhance its oral bioavailability by targeting the lymphatic system. The results demonstrated the enhanced oral bioavailability (3.56-fold) for lopinavir-loaded SLNs compared to the free drug due to higher lymphatic drug transport \[121\]. In another study, Kumar and his colleagues developed a
Table 2. Summary of nanomedicine to improve the biopharmaceutical performance of repurposed drug having potential in COVID-19 management.

| Nanocarrier | Drug       | In-vitro/in-vivo model | Outcomes                                                                 | References |
|-------------|------------|------------------------|---------------------------------------------------------------------------|------------|
| Liposome    | Lopinavir  | \(\text{In-vitro}\)    | – Significantly higher bioavailability in spleen and thymus.              | [119]      |
|             | Ritonavir  | Huh7.5, human hepatoma cells | – Significantly enhanced bioavailability.                                  | [120]      |
| Liposome    | Lopinavir  | Caco-2                 | – Significantly enhanced bioavailability (-higher lymphatic drug transport). | [121]      |
| SLNs        | Ritonavir  | in-vitro               | – Improved intestinal lymphatic target specificity.                        | [122]      |
|             | Lopinavir  | Wistar albino rats     | – Improved bioavailability (6.98-fold) compared to drug suspension.       | [123]      |
| NLCs        | Lopinavir  | Caco-2                 | – Significantly enhanced cellular uptake.                                 | [124]      |
|             | Lopinavir  | Wistar albino rats     | – Improved peak plasma concentration of the drug.                         | [125]      |
| SNEDDS      | Lopinavir  | Wistar albino rats     | – Enhanced drug entrapment efficiency.                                    | [126]      |
|             | Efavirenz  | HeLa cells             | – Significantly enhanced bioavailability (2.97 and 1.54-folds)             | [127]      |
|             | Lopinavir  | H9 T cells             | – Significantly enhanced drug entrapment efficiency.                      | [128]      |
| Polymeric NPs | Lopinavir | \(\text{In-vitro}\)    | – Significantly enhanced drug entrapment.                                  | [129]      |
|             | Ribavirin  | \(\text{Huh7.5, human hepatoma cells}\) | – Enhanced cellular uptake.                                               | [130]      |
|             | Ribavirin  | \(\text{HepG2 cells}\) | – Negligible accumulation into RBCs.                                      | [131]      |
| Polymeric micelles | Lopinavir | \(\text{In-vitro}\)    | – Enhanced stability-Improved entrapment efficiency.                      | [132]      |
| TPGS micelles | Lopinavir | \(\text{New Zealand rabbits}\) | – Enhanced drug dissolution.                                               | [133]      |

SLN of ritonavir to target intestinal lymphatic vessels and to improve its bioavailability by oral route. In-vitro pharmacokinetic studies in Wistar rats indicated the enhanced absorption of SLNs in the spleen and thymus [112]. Similarly, Javan et al (2017) reported the enhanced in-vitro drug release from ritonavir-loaded SLNs. Furthermore, the developed formulation actively maintained the inhibition of virus production [123]. Ravi and his co-workers investigated the hybrid design of lopinavir-loaded SLNs and compared in-vivo pharmacokinetic
has 2.97 and 1.54-folds higher bioavailability than pure LPV and LPV and propylene glycol as co-surfactant.

Successful pilot-plant production of the SNEDDS of ritonavir improved absorption and bioavailability, and lymphatic uptake solubility and high loading efficiency in Wistar rats with marketed lopinavir.

The involvement of lymphatic route in the absorption of NPs with an aqueous phase under gentle stirring demonstrated the enhanced drug release from the NPs loaded suppositories than those in the fatty base. suppositories were developed by Katata-Seru et al. The results demonstrated the enhanced drug release from the NPs loaded suppositories than those in the fatty base.

Polymeric nanoparticles are basic nano-vector fabricated by using various biocompatible polymeric matrix that can be natural, synthetic, or semi-synthetic polymer.

Polymeric nanoparticles are basic nano-vector fabricated by using various biocompatible polymeric matrix that can be natural, synthetic, or semi-synthetic polymer. The drug molecules are either incorporated in the core, adsorbed, embedded in the matrix, or covalently attached. Polymeric nanoparticles offer the advantage of enhanced stability than liposomes in biological fluids and under storage, controlled release, enhanced cellular uptake, reduced toxicity, and their potential to be used as theranostics.

Polymeric NPs are prepared by various means such as double-emulsion solvent evaporation, emulsion diffusion, coacervation, nanoprecipitation, ionic gelation, spray-drying, and supercritical fluid technology. In a study carried out by Shibata et al. (2013), poly- l-lactide-co-glycolic acid (PLGA) nanoparticles of efavirenz and lopinavir/ritonavir were designed. The results demonstrated the enhanced drug entrapment efficiency (>79%) and exhibited efficient in-vitro cellular uptake by HeLa cells and HT9 cells with significant inhibition of viral infection and transduction. Lopinavir-loaded poly-e-caprolactone (PCL) nanoparticles were prepared by Ravi et al. (2015). The result exhibited the high entrapment efficiency (93.9%) and in-vitro drug release study showed bi-phasic sustained release behavior of drugs from NPs. Also, a pharmacokinetic study in Wistar rats specified an increase in oral bioavailability of the drug by 4-folds. From tissue distribution studies, significant accumulation of drug-loaded NPs in tissues like the liver and spleen indicated the possible involvement of lymphatic route in the absorption of NPs. Recently Eudragit lopinavir NPs loaded suppositories were developed by Katata-Seru et al. (2020) to improve the bioavailability and overcome the problem encountered through oral administration emanating from poor solubility. The in-vitro release study demonstrated the enhanced drug release from the NPs loaded suppositories than those in the fatty base. In the study carried out by Abo-zeid, ribavirin was the drug of choice for the fabrication of polymeric nanoparticles. The results demonstrated the enhanced in-vitro cellular uptake by Huh7.5 cell. In another study carried out by Ishihara et al. (2014), ribavirin-loaded biodegradable NPs were developed using a blend of poly (dl-1-lactic acid) homopolymer and arabinogalactan (AG)–poly(l-lysine) conjugate. The developed NPs were efficiently internalized by HepG2 cells. Besides, in-vivo study in female C57BL/6N mice indicates that ribavirin was accumulated in the liver.
4.2.2. Polymeric micelles

Polymeric micelles are nanometric colloidal structures formed by the self-association of amphiphilic block copolymers beyond the critical micellar concentration when they are added to an aqueous solvent [153]. The hydrophilic segment form the outer shell, and hydrophobic segment form the spherical inner core, that helps in the encapsulation of poorly water-soluble drug [154, 155]. Polymeric micelles offer the advantage of biocompatibility, minimum toxicity, core–shell structure, micellar association, and comparatively enhanced stability, which make them suitable for use in drug delivery [102, 109, 153]. Functionalization of an outer hydrophilic shell with a specific ligand such as folate, monoclonal antibodies, and monosaccharides has provided the advantage of active targeting or pH/temperature-responsive nanovector [102, 154, 155]. Recently Chaudhari et al (2020) demonstrated the fabrication, optimization, and evaluation of lopinavir–loaded polymeric micelles using block copolymer (Pluronic F68, Pluronic F127) and Tween 80 as a co-solvent [133]. Enhanced drug loading and entrapment efficiency were observed with the developed formulation [133]. Mahajan et al (2020) formulated lopinavir–loaded Vitamin E-TPGS micelles intended for oral administration [134]. The developed lopinavir micelles exhibited enhanced drug dissolution. In-vivo pharmacokinetics study in New Zealand rabbit demonstrated significantly enhanced bioavailability (3.17) of the drug compared to lopinavir suspension [134].

5. Current challenges and further directions

The whole world is fighting a relentless war against a deadly and highly infectious SARS-CoV-2 with substantially greater spreading potential. Currently, no medication is clinically approved or particularly indicated for its treatment except symptomatic treatment and/or supportive care against this pandemic disease. Indeed, some COVID-19 vaccines are recently getting available in the market as prophylactic therapy against this highly infectious disease. Moreover, long-term human safety data is yet to be collected and analyzed to establish the overall safety profile of the COVID-19 vaccine. From a therapeutic point of view, the repurposing of some potential antiviral drugs is presently the main focus of research. Some other pre-existing drugs with significantly higher in-vitro and in-vivo efficacy against COVID-19 have been explored for reasonable safety and pharmacokinetic profile in humans. However, there are various challenges in its development and application. The coronaviruses are RNA viruses with variability. Therefore, new variants of coronaviruses with novel structures easily appear. The pre-existing drugs may not be similarly effective for these new variants of coronavirus or have only weak effects. Various therapeutics have high EC50/Cmax ratios in the clinic and are prone to severe adverse effects (like high-dose ribavirin might be associated with hemolytic anemia, neutropenia, and cardiopulmonary distress). Furthermore, virus research is highly risky and challenging to meet the biosafety requirements for general experimental conditions. Thus screening techniques and suitable animal experimental platforms are limited. There are also some challenges in clinical trial resources and enrollment of patients with related diseases into clinical study. Though research of this disease-causing agent is mainly based on the findings of genome sequencing and bioinformatics, certain screening models (such as SARS and MERS virus-infected cells), and few small mechanisms based on different mechanisms of action (like inhibitors nucleic acid synthesis, protease inhibitors, and polymerase inhibitors) have been established. Subsequently, with low specificity of research and investigation related to this disease, there is a lack of strong clinical evidence to establish the efficacy of broad-spectrum antiviral therapeutics against this virus. Further extensive research is required and attention should be given to certain toxic effects.

Further research can be focused to achieve multimodal therapeutics for site-specific, concurrent delivery of multiple antiviral drugs. The development of these advanced forms of drug delivery system for antiviral therapeutics is usually more complex than the traditional drug delivery system. Among the few obstacles in the development of these promising technology includes the complexities in large-scale production. Optimized fabrication of nanocarrier system to encapsulate the potential therapeutics using the quality-by-design approach to point out the critical processing factor and material attributes of contents is a major concern. Furthermore, a comprehensive understanding related to the structural morphology of COVID-19, its virulence, and transmission is crucial for the formulation scientist to design a novel drug delivery against it. Detailed investigations are required to reveal the interface between COVID-19 and nanomedicine for the optimized design of novel therapeutics.

Data availability statement

No new data were created or analysed in this study.
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