Potency, Safety, and Pharmacokinetic Profiles of Potential Inhibitors Targeting SARS-CoV-2 Main Protease

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Effective, safe, and pharmacokinetically suitable drugs are urgently needed to curb the ongoing COVID-19 pandemic. The main protease or 3C-like protease (Mpro or 3CLpro) of SARS-CoV-2 is considered an important target to formulate potent drugs corresponding to its crucial role in virus replication and maturation in addition to its relatively conserved active site. Promising baseline data on the potency and safety of drugs targeting SARS-CoV-2 Mpro are currently available. However, preclinical and clinical data on the pharmacokinetic profiles of these drugs are very limited. This review discusses the potency, safety, and pharmacokinetic profiles of potential inhibitors of SARS-CoV-2 Mpro and forward directions on the development of future studies focusing on COVID-19 therapeutics.

Keywords: potency, safety, pharmacokinetics, inhibitors, SARS-CoV-2, main protease, COVID-19

INTRODUCTION

Coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is causing significant social, economic, and political disturbances worldwide. The number of cases is above seventy-nine million with a toll of death surpassing 1.74 million (https://www.worldometers.info/coronavirus/) as of December 24, 2020. The presence of asymptomatic carriers, various modes of transmission, limitation of point-of-care diagnostic facilities especially in resource-limited countries, and lack of globally approved vaccines and antiviral drugs (Cascella et al., 2020; Covid et al., 2020; Mekonnen et al., 2020; Patel et al., 2020; Wang et al., 2020b; Zhang et al., 2020d) are among others worsening the challenge.

Although remdesivir is currently approved by the FDA of the USA for COVID-19 treatment (Beigel et al., 2020), conflicting clinical results have been reported. Remdesivir helps fast recovery of moderate and severely affected patients but its clinical effect on nonmechanically ventilated severely affected patients is optimal (Elsawah et al., 2020). This indicates that the treatment of COVID-19 is still medically unmet requiring further efforts. Currently, patient management is primarily dependent on symptomatic treatment and respiratory support including intensive care in case of complicated disease (Cascella et al., 2020; Chen et al., 2020; Gattinoni et al., 2020). Fifteen drugs (chloroquine, hydroxychloroquine, lopinavir, ritonavir, nafamostat, camostat, famotidine, umifenovir, nitazoxanide, ivermectin, corticosteroids, tocilizumab, sarilumab, bevacizumab, and...
Many potential drugs have been showing effective antiviral activity in vitro and in vivo (Ullrich and Nitsche, 2020). Pyridones containing peptidomimetic alpha-ketoamide inhibitors 13a and 13b are amongst the promising drugs that exhibited strong SARS-CoV-2 inhibition. In human Calu-3 lung cells infected with SARS-CoV-2, 13b showed good inhibitory activity with a half-maximal effective concentration (EC50) value of 4–5 μM (Zhang et al., 2020a, Zhang et al., 2020b). However, the in vivo potency and safety of 13a and 13b are not reported yet, which needs further investigation.

Flavonoids and quercetin showed moderate antiviral activity in both in vitro and in vivo assays (Shaffer, 2020). In Vero cells, flavonoids and quercetin displayed effective inhibition of SARS-CoV-2 replication and infection. Ebselen demonstrated more potency (EC50 < 5 μM) over N3 as the antiviral activity of N3 was moderate with a relatively higher EC50 value >16 μM (Jin et al., 2020a).

Aldehyde-based drugs 11a and 11b were synthesized being suitable to bind and inhibit SARS-CoV-2 MPro with respective 100% and 96% in vitro inhibition of the MPro at 1 μM. Regarding their antiviral activity, plaque assay in cell culture showed that 11a and 11b demonstrated excellent anti-SARS-CoV-2 infection activity with very low EC50 values <1 μM (Dai et al., 2020). Carmofur is an antineoplastic drug currently considered for COVID-19 treatment. Carmofur is reported to moderately inhibit SARS-CoV-2 infection in Vero E6 cells with an EC50 value of >20 μM (Jin et al., 2020b).

Rathnayake et al. (Rathnayake and Zheng, 2020) demonstrated the potency of compounds in SARS-CoV-2 infected Vero E6 cells via targeting the main protease. Accordingly, the synthesized compounds showed effective inhibition of virus replication with EC50 values between 0.15 and 0.9 μM. The activity of synthesized compounds was also confirmed by the significant difference in the virus plaque-forming units (PFU) observed in the presence and absence of MPro inhibitors in cell culture. Plaque assays and virus reduction assays indicated that GC-373 and GC-376 demonstrated effective inhibition and reduction of SARS-CoV-2 RNA copies in Vero E6 cells with EC50 values between 0.9 and 1.5 μM. Comparatively,
### TABLE 1 | Description of the potency, safety, and pharmacokinetic profiles of drugs targeting SARS-CoV-2 Mpro.

| Drug                        | Potency (EC_{50}, µM) | Safety (CC_{50}, µM) | Pharmacokinetic profile | Remark                                                                 |
|-----------------------------|-----------------------|----------------------|-------------------------|-------------------------------------------------------------------------|
|                            |                       |                      | T_{1/2} (hours) | C_{max} (ng/ml) | Clearance (ml/min/kg) |                                                                 |
|                            |                       |                      |              |              |                      |                                                                 |
| 13a (Zhang et al., 2020a, Zhang et al., 2020b.) | 4–5^a |                    | 1.0 ± 0.1 | 334.5 ± 109.2 | 565.6 ± 61.0 | Administered in CD-1 mice (20 mg/kg)^bc |
| 13b (Zhang et al., 2020a, Zhang et al., 2020b.) | 4–5^a |                    | 1.8 ± 0.5 | 126.2 ± 31.0 | 131.6 ± 26.0 | Administered in CD-1 mice (3 mg/kg)^bc |
| Ebselen (Jin et al., 2020a; Masumoto et al., 1997.) | 4.67^a | > 100^a             | 2.1 | 14780^a |                      | Activity in rats |
| NO (Jin et al., 2020a)       | 16.77                 | > 130                |              |              |                      | Activity in Vero cells |
| Carboxol (Jin et al., 2020a.) | 20.61                 | > 200                |              |              |                      | Activity in Vero cells |
| 11a (Dai et al., 2020.)      | 24.0 ± 3.61           | 133 ± 12             | 4.27 ± 1.23^b | 2394 ± 288^b | 17.4 ± 2.76^b | Administered in CD-1 mice (5 mg/kg) |
| 11b (Dai et al., 2020.)      | 0.53 ± 0.01^a         | > 189                | 5.21 ± 1.35^b | 3019 ± 665^c  | 20.6 ± 2.0^b  | Administered in CD-1 mice (5 mg/kg) |
| 6e (Rathnayake and Zheng, 2020.) | 0.15                 | 63.3 ± 2.3           |              |              |                      | Activity in Vero E6 cells |
| GC-373 (Yung and Khan, 2020.) | 1.50 ± 0.30          | > 200                |              |              |                      | Activity in Vero E6 cells |
| GC-376 (Yung and Khan, 2020.) | 0.90 ± 0.20          | > 200                |              |              |                      | Activity in Vero E6 cells |
| Roceprevir (Ma et al., 2020; Treiteli et al., 2012.) | 1.95 ± 1.62^g         | > 100^a              | 6.51 | 914 | 157^a | Activity in severe hepatic failure patients |
| Telaprevir (Gammeltoft et al., 2020; Garg et al., 2013) | 40^f | > 432^c             | 3.8 ± 0.8 | 1899 |                      | Activity in healthy human volunteers |
| Narlaprevir (Arasappan et al., 2010; de Bruin et al., 2010; Isakov et al., 2016.) | 0.04 | 269^d                | 9.3 | 1,630 |                      | Activity in chronic HCV patients/ cirrhosis |
| Grazoprevir (Gammeltoft et al., 2020.) | 20          | 133                 |              |              |                      | Activity in Huh7.5 cells |
| Simprevir (Gammeltoft et al., 2020; Ouwerkerk-Mahadevan et al., 2015.) | 14^c | 35^c                | 2,588 |              |                      | Activity in renally impaired patients |
| 4-CMBA (Brown et al., 2020.) | 0.095 ± 0.007         |                      |              |              |                      | Activity in Vero 76 cells |
| Ementine (Choy et al., 2020b) | 0.46                 |                      |              |              |                      | Activity in Vero 6 cells |
| Homororringtonine (Choy et al., 2020b) | 2.55 |                      |              |              |                      | Activity in Vero 6 cells |
| Baicalin (Su et al., 2020.) | 10.27                | > 200                |              |              |                      | Activity in Vero E6 cells |
| Baicaiein (Su et al., 2020.) | 1.69                 | > 200                |              |              |                      | Activity in Vero E6 cells |
| Remdesivir (Hu et al., 2020; Humeniuk et al., 2020; Söngel et al., 2020; Wang et al., 2020a) | 0.77^e | > 100^a             | 1.05 ± 0.08 | 4420^d | 719^d | Activity in healthy humans |
|                                | 0.80 ± 0.08           |                      | 1.11^f | 19800^h | 257^h | Administered in a COVID-19 patient (225 mg/kg) |
| Nafamostat (Wang et al., 2020a.) | 22.50^d | > 100                | 13.81 | 2000 | 3.81^a | Activity in a pharmacokinetic model of white and Chinese populations |
| Lopinavir (Dandache et al., 2007; Gorbalenya et al., 2020; Zhang et al., 2020c.) | 0.019 ± 0.001^i | 80.82^g | 3.40 ± 0.96 | 710 |              | Activity in HIV-1 patients |
| Ritonavir (Murphy et al., 2001; Zhang et al., 2020c.) | 0.07^* | 94.7^e             | 2.7 ± 1.09 | 1,370 | 0.25 ± 0.09^f | Activity in healthy volunteers |
| AG7404 (Zhang et al., 2020c.) | > 100^2             |                      |              |              |                      | Activity in Vero E6 cells |
| Imatinib (Dyall et al., 2014; Weston et al., 2020.) | 9.82 | > 30.86             |              |              |                      | Activity in Vero E6 cells |
| Ribavirin (Cinatl et al., 2003.) | >1000^3            |                      |              |              |                      | Activity in Vero cells |

**Key:** 4-CMBA: 4-chloromercuribenzoic acid, FRET: fluorescence resonance energy transfer, ip: intraperitoneally, iv: intravenously, sc: subcutaneously, if: infusion, or: orally c: experiment done in cell culture, *: measured in µg/mL, #: measured in L/h/kg, $: measured in mg/L, and £: measured in mmol/kg. The chemical formula, IUPAC name, and the chemical structure of potential SARS-CoV-2 Mpro inhibitors are described in Supplementary Table S1.
GC-376 showed stronger inhibitory activity over GC-373 evidenced by a very low EC\textsubscript{50} value below 1 µM (Vuong and Khan, 2020).

According to Ma et al. (2020), boceprevir, GC-376, and calpain inhibitors II and XII also demonstrated effective inhibition of SARS-CoV-2 replication in Vero 76 cells. The FDA approved HCV drug boceprevir that showed an effective viral reduction with an EC\textsubscript{50} value below 2 µM while calpain inhibitor II and GC-376 demonstrated a higher EC\textsubscript{50} value above 3 µM. Among these, calpain inhibitor XII exhibited the most potent antiviral activity against SARS-CoV-2 with a very low EC\textsubscript{50} value below 1 µM. Further, GC-376 and boceprevir showed effective inhibition of SARS-CoV-2 replication in Vero cells. GC-376 exhibited a strong inhibition potency more than boceprevir (average EC\textsubscript{50} values: 0.70 µM for GC-376 and 15.57 µM for boceprevir). The authors reported that a combination of 1 µM GC-376 and 1 µM remdesivir can completely inhibit SARS-CoV-2 in vitro replication (Choy et al., 2020).

Besides, GC-376 was also reported to effectively inhibit SARS-CoV-2 infection in Vero E6 cells (Hung et al., 2020) where a plaque assay stated a 0.49 ± 0.35 µM EC\textsubscript{50} value of GC-376. GC-376 analogs (UAWJ246, UAWJ247, and UAWJ248) also produced effective inhibition of SARS-CoV-2 in Vero cells where UAWJ247 demonstrated the strongest inhibition (Sacco et al., 2020). Another study also reported excellent potency of GC-376 against SARS-CoV-2 with an EC\textsubscript{50} value of 0.91 ± 0.03 µM in Vero E6 cells (Hung et al., 2020). This drug (GC-376) is known to exhibit a strong potency against several other coronaviruses in cell lines (Kim et al., 2012). Brown et al. (2020) used a fluorescence resonance energy transfer (FRET) biosensor to evaluate the potency of 65 compounds against SARS-CoV-2 M\textsuperscript{pro}. Among these, ebselen and 4-chloromercuribenzoic acid demonstrated the strongest virus inhibition in the presence and absence of Triton X-100. Baicalin and baicalein are noncovalent nonpeptidomimetic compounds exhibiting effective binding and inhibition of SARS-CoV-2 M\textsuperscript{pro} with baicalein showing the strongest potency (EC\textsubscript{50} value <2 µM) close to chloroquine and remdesivir (Su et al., 2020). An in silico study predicted remdesivir and nafamostat bind on the catalytic dyad of the M\textsuperscript{pro} (Chakraborti et al., 2020) with potent antiviral activities in cells (Wang et al., 2020a).

Safety

The in vivo safety of proposed drugs for COVID-19 targeting the M\textsuperscript{pro} is not explicitly reported. But the in vitro half cytotoxic concentration (CC\textsubscript{50}) values of some drugs are reported. Drugs 11a and 11b showed good safety to cells with a CC\textsubscript{50} value of >100 µM in vitro. Specifically, 11a showed no obvious toxicity in rats and dogs given at different doses for seven days (Dai et al., 2020). Studies reported that ebselen has very low toxicity in rats and dogs given at different doses for seven days (Dai et al., 2020). Studies reported that ebselen has very low toxicity in rats (Renson et al., 1982) and is safe for humans in clinical trials (Lynch and Kil, 2009; Masaki et al., 2016; Kil et al., 2017). N3 and cinanserin are also reported to be safe to Vero cells with a CC\textsubscript{50} value of >100 µM with cinanserin exhibiting comparatively low toxicity (CC\textsubscript{50} value >200 µM) (Jin et al., 2020a). Carmofur also demonstrated low toxicity in Vero E6 cells with an average CC\textsubscript{50} value of >133 µM (Jin et al., 2020b). In cell culture, although reported to have high potency, 6e exhibited relatively higher toxicity to cells with a CC\textsubscript{50} value below 100 µM. On the contrary, other compounds (6c, 6h, and 6i) demonstrated an acceptable level of toxicity with CC\textsubscript{50} values >100 µM (Rathnayake and Zheng, 2020).

Feline coronavirus drugs targeting SARS-CoV-2 M\textsuperscript{pro} (GC-373 and GC-376) demonstrated very low toxicity in Vero E6 cells with CC\textsubscript{50} values above 200 µM (Vuong and Khan, 2020). Boceprevir, GC-376, and calpain inhibitors II and XII also demonstrated acceptable level of toxicity with CC\textsubscript{50} values above 100 µM in cell culture (Ma et al., 2020). A study showed that boceprevir and GC-376 did not cause obvious in vitro toxicity to Vero cells (Choy et al., 2020). Interestingly the CC\textsubscript{50} value of GC-376 is higher in Vero E6 cells indicating its low toxicity (Hung et al., 2020). GC-376 analogs UAWJ246, UAWJ247, and UAWJ248 also demonstrated very low toxicity to Vero cells where UAWJ246 and UAWJ248 displayed a CC\textsubscript{50} value >250 µM while the CC\textsubscript{50} value of UAWJ247 was between 179 and 189 µM (Sacco et al., 2020). The safety of the anticipated drugs should be elaborately investigated for a better understanding of their toxicity properties.

Baicalin and baicalein demonstrated very low cytotoxicity in Vero E6 cells with CC\textsubscript{50} values > 200 µM (Su et al., 2020). Thimerosal, phenylmercuric acetate, hematoporphyrin, chloralin, plumbagin, Evans blue, and Chicago sky blue showed effective inhibition against SARS-CoV-2 M\textsuperscript{pro} (Coelho et al., 2020). Earlier, the safety of plumbagin, Evans blue, and Chicago sky blue measured by median lethal dose (LD\textsubscript{50}) was reported to be 16, 340, and 2,260 mg/kg administered through different routes in mice/rats (Weinberg et al., 1951; Krishnaswamy and Purushothaman, 1980; Balzarini et al., 1986). Known drugs, remdesivir and nafamostat, also showed acceptable cytotoxicity in cell culture (Wang et al., 2020a; Wang et al., 2020b); however, with increasing clinical application, remdesivir is showing adverse effects in COVID-19 patients (Fan et al., 2020). Lopinavir/ritonavir monotherapy was also found to be toxic with poor clinical effects in mild/moderate COVID-19 patients (Li et al., 2020b).

Pharmacokinetic Profiles

Studies reporting the in vivo pharmacokinetic properties of prospective COVID-19 drugs targeting SARS-CoV-2 M\textsuperscript{pro} are scarce. Alpha-ketoamide drug 13a demonstrated good metabolic stability with low intrinsic clearance rates in mouse and human microsomes. When administered subcutaneously in CD-1 mice with different doses, 13b showed higher plasma half-life (T\textsubscript{1/2}) and a lower clearance rate than 13a. On the other side, 13a was better concerning the average amount in plasma with a higher plasma maximal concentration (C\textsubscript{max}) value above 334 ng/ml (Zhang et al., 2020a, Zhang et al., 2020b).

More data are available for drugs 11a and 11b which exhibited different pharmacokinetic properties when administered in different routes in CD-1 mice. 11a showed better plasma T\textsubscript{1/2} when administered to mice intraperitoneally than intravenously (5 mg/kg). Comparatively, 11a displayed a high C\textsubscript{max} and a good bioavailability when administered intraperitoneally. Its metabolic stability, measured by the rate of clearance (ml/min/kg), was also
good. 11b also showed good pharmacokinetic properties when administered intraperitoneally (20 mg/kg), subcutaneously (5 mg/kg), and intravenously (5 mg/kg). More specifically, 11b showed good bioavailability when given both intraperitoneally and subcutaneously (Dai et al., 2020).

When administered intravenously, 11b showed faster clearance and shorter half-life indicating the suitability of 11a through this route. Further pharmacokinetic assessment of 11a showed, when administered intravenously (10 mg/kg) to SD rat, that it demonstrated low clearance (4.01 ml/min/kg), long T1/2 (7.6 h), and high 3-min maximum concentration (81,500 ng/ml). Conversely, 11a, when administered intravenously (5 mg/kg) to beagle dog, exhibited higher clearance (5.80 ml/min/kg), shorter T1/2 (5.5 h), and lower 3-min maximum concentration (21,900 ng/ml) (Dai et al., 2020) indicating better pharmacokinetic profiles in SD rat administered at high dose than beagle dog. Further, the authors also reported that 11a exhibited no obvious toxicity in rats and dogs administered intravenously at appropriate doses. It is considered, due to safety issues, that intravenous administration is more appropriate where safety issues, that intravenous administration is more appropriate where

Several clinically approved drugs showed effective binding on SARS-CoV-2 Mpro with possible antiviral activities. Among these, HCV NS3/4A protease inhibitors (sovaprevir, vaniprevir, glecaprevir, boceprevir, simeprevir, paritaprevir, danoprevir, and grazoprevir) (Bañà et al., 2020), HIV protease inhibitors [nelfinavir (Xu et al., 2020) and lopinavir/ritonavir (Nukoolkarn et al., 2008)], immune modulators (vinflunine, vindesine, and topotecan) (Chakraborti et al., 2020), and other drugs including colistin (antibiotic), valrubicin (antitumor), ictibant (indicated for hereditary angioedema), bepotastine (prescribe for rhinitis), caspofungin (antifungal), perphenazine (antipsychotic) (Liu and Wang, 2020), bromocriptine (a dopamine antagonist), ergotamine (antimigraine), bicinegravir (antiviral), antibacterial agents (oxytetracycline, tigecycline, and cefotolozane) (Chakraborti et al., 2020), viz. D2 receptor antagonist, HMG-CoA inhibitors, HIV reverse transcriptase and protease inhibitors, anticancer agents, folate inhibitors, and imatinib (Balaramanavar et al., 2020) showed effective binding on the Mpro. Although their suitability in COVID-19 patients is to be determined, the potency, safety, and/or pharmacokinetic properties of known drugs inhibiting SARS-CoV-2 Mpro are reported before, which is briefly described in Table 1.

**DISCUSSION AND PERSPECTIVES**

Determining the potency, safety, and pharmacokinetic profiles of drugs and applying it into clinical practice is the ultimate aim of drug discovery. Determining the binding affinity and efficiency of the anticipated drugs with the target, evaluating its target inhibitory activity, and assessing its role in curbing infection in vitro are all early stages of the process of drug discovery. The drug should be evaluated in model organisms in vivo and should be tested in a cohort of humans under clinical trials which is the most challenging step to achieve. The physiological process in humans is quite complex which affects the pharmacokinetic and pharmacodynamic properties of the anticipated drugs. The final goal in therapeutic medical research is to find an effective, safe, and pharmacokinetically suitable drug with minimum side effects on human tissues. This is quite challenging and that is why, although a couple of months passed, there is no globally approved specific antiviral drug yet to treat the COVID-19 pandemic.

Scientists have been investigating the potency and safety of old and new drugs through studying the ability of the drugs to specifically bind and inhibit target proteins and control virus replication. The emergence of tremendous publications on COVID-19 therapy is proof of the ongoing efforts in discovering potential drugs (Bein et al., 2020; Li et al., 2020; McCreary and Pogue, 2020; Sanders et al., 2020). However, only a small fraction of studies presented data on the preclinical and clinical potency, safety, and pharmacokinetic properties of drugs where the progress is more infant in drugs targeting SARS-CoV-2 Mpro as most studies lack experimental validation where only scientific simulation data are available.

Urgent COVID-19 therapeutic options are desired by the community (de Almeida et al., 2020). In this regard, based on previous therapeutic experience with SARS-CoV and MERS-CoV, there has been a substantial inquisitiveness in the repurposing of approved antiviral drugs (for example, drugs used to treat HIV, HBV, HCV, filoviruses, and influenza) and development of new drugs for COVID-19 (Artese et al., 2020; Liu and Wang, 2020). Apart from the ongoing struggles in searching for effective drugs for COVID-19, challenges are facing these efforts (Ghaebi et al., 2020). Among these, urgency is of significant factor which is exacerbated by the time-consuming and expensive nature of the data acquisition process in physical experiments. Intriguingly, the application of computational simulations and drug repurposing programs significantly alleviates the problem through providing basic data; however, whether these drugs pass clinical trials is another headache to the scientific world which puts the progress of finding clinically applicable COVID-19 drugs at its early stage. A mutant coronavirus was reported on November 5, 2020 in mink populations in Denmark which can spread to humans (Lesté-Lasserre, 2020). Besides, a recent study by Hou et al. (Wu et al., 2020) reported that spike protein D614G SARS-CoV-2 variant demonstrates more efficient infection, replication, and competitive fitness than the wild type indicating that the evolution of the virus could make the drug and vaccine discovery efforts more challenging.

Here, we discussed the potency, safety, and pharmacokinetic profiles of drugs halting SARS-CoV-2 infection through targeting the Mpro. Several drugs including alpha-ketoamide inhibitors, aldehyde-based inhibitors, N3, ebselen, carmofur, Feline coronavirus inhibitors (GC-373 and GC-376), GC-376 analogs, calpain inhibitors II and XII, and clinically approved anti-HCV and HIV drugs have been investigated for their potential anti-SARS-CoV-2 activity. Here we observed that most studies report
only the in vitro pharmacokinetic profiles of potential drugs are very limited. Drugs 13a, 13b, 11a and 11b, GC-376, GC-373, 6e, boceprevir, narlaprevir, bicaudaline, remdesivir, calpain inhibitors II and XII, and UAWJ247 showed a very low EC₅₀ value and a high CC₅₀ value above 100 μM (except 6e with a CC₅₀ value below 65 μM) indicating their potency and safety. However, data on the in vivo pharmacokinetic profiles of new drugs were reported only for 13a, 13b, 11a, and 11b. Accordingly, although the currently available data are limited to decide the best new drug for further investigation, 11a demonstrated better potency, safety, and in vivo pharmacokinetic activity (Table 1). Lack of sufficient data especially on new drugs hampered us to discuss the potency, safety, and pharmacokinetic characteristics of potential drugs impeding SARS-CoV-2 infection through inhibiting the Mₚro in detail. Drug repurposing and the use of previously known drugs are very important to speed up the discovery of putative therapeutic options for new diseases during urgent times. As data on the pharmacokinetic profiles of known drugs are comparatively available, trying this option could be ultimately helpful provided that their suitability for COVID-19 patients should be determined. Despite limited data on the pharmacokinetic profiles of drugs, this review provides a glimpse into choosing the best new and/or repurposed drugs for further investigation.

Generally, current therapeutic options proposed to treat COVID-19 are mostly based on the results of in vitro studies, observational studies, and clinical trials (Fernandes et al., 2020); perhaps, computational predictions also account for a big proportion of these studies. Specifically, most studies on drugs targeting the main protease of SARS-CoV-2 present only data related to the in vitro potency and safety while in vivo pharmacokinetic profiling is very limited. The main protease is a crucial enzyme for virus replication and maturation (Ziebuhr et al., 2000; Jain and Mujwar, 2020) and has a relatively conserved active site (Stoermer, 2020; Ulrich and Nitsche, 2020) which makes it considered as a potential drug target (Naqvi et al., 2020).

Remarkably, there are promising baseline data on potential inhibitors of SARS-CoV-2 Mₚro. Therefore, future research on drugs targeting SARS-CoV-2 Mₚro should escape from preliminary computational, in vitro, and in vivo studies and advance to preclinical and clinical applications. Besides, cautious use of known broad-spectrum drugs in terms of potency, safety, selectivity, suitability, and binding affinity is also recommended. More importantly, COVID-19 therapeutic studies should consider the emergence of new SARS-CoV-2 variants due to virus evolution as the occurrence of 1-2 mutations every month is estimated (Duchene et al., 2020).

**AUTHOR CONTRIBUTIONS**

HM conceived the topic and wrote the original draft. All authors read and approved the final draft.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.630500/full#supplementary-material.

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