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REVIEW ARTICLE

COVID-19 therapeutics: Clinical application of repurposed drugs and futuristic strategies for target-based drug discovery

Sunny Kumar [a], Malini Basu [b,], Pratyasha Ghosh [c], Uttam Pal [a], Mrinal K. Ghosh [a,*]**

[a] *Cancer Biology and Inflammatory Disorder Division, Council of Scientific and Industrial Research-Indian Institute of Chemical Biology (CSIR-IICB), TRUE Campus, CN-6, Sector–V, Salt Lake, Kolkata-700091 & 4, Raja S.C. Mullick Road, Jadavpur, Kolkata 700032, India*
[b] *Department of Microbiology, Dhruba Chand Halder College, Dakshin Barasat, West Bengal 743372, India*
[c] *Department of Economics, Bethune College, University of Calcutta, Kolkata 700006, India*

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Abstract Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes the complicated disease COVID-19. Clinicians are continuously facing huge problems in the treatment of patients, as COVID-19-specific drugs are not available, hence the principle of drug repurposing serves as a one-and-only hope. Globally, the repurposing of many drugs is underway; few of them are already approved by the regulatory bodies for their clinical use and most of them are in different phases of clinical trials. Here in this review, our main aim is to discuss in detail the up-to-date information on the target-based pharmacological classification of repurposed drugs, the potential mechanism of actions, and the current clinical trial status of various drugs which are under repurposing since early 2020. At last, we briefly proposed the probable pharmacological and therapeutic drug targets that may be preferred as a futuristic drug discovery approach in the development of effective medicines.

* Corresponding author.
** Corresponding author.
E-mail addresses: drmalini.basu@gmail.com (M. Basu), mrinalghosh@iicb.res.in, mrinal.res@gmail.com (M.K. Ghosh).
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Introduction

On December 1, 2019, the first case of coronavirus was officially reported in Wuhan, China. WHO named it 2019 novel coronavirus (2019-nCoV) on December 29, 2019; later on February 11, 2020, it was named coronavirus disease 2019 (COVID-19). Immediately after the first detection in Wuhan, coronavirus cases were reported in other countries as well. Travel restrictions and quarantine measures were placed in many affected countries to restrict the spread of this disease.[1–3] The possibility of COVID-19 infection was suspected in people having a clinical illness with or without pneumonia, exposure history, and other risk factors. Although the number of new cases in some nations is declining with the increasing global spread, the scope and trajectory of infection elsewhere remain a challenge for the rest of the world. Patients with a mild clinical presentation may not require hospitalization but should be monitored for worsening, especially during the first two weeks of illness as the incubation period of COVID-19 infection is about 2—14 days. Social distancing is recommended to minimize the potential exposure through community spread from disease hotspots.[4,5] Rapid ELISA and RT-PCR-based tests with available suitable diagnostic kits for the detection of infection and identification of hotspots are the crucial events to prevent the spread of the disease.[6] A COVID-19 patient with a late-stage disease or with comorbid health conditions, such as heart or lung dysfunction or cardiac or cerebral ischemia requires mechanical ventilation or even extracorporeal membrane oxygenation (ECMO) support, although the prognosis is likely to be dismal.[7,8]

Coronaviruses cause common colds with major symptoms, such as fever and sore throat, occurring primarily in the winter and early spring. They can cause pneumonia (either direct viral pneumonia or secondary bacterial pneumonia), bronchitis (either direct viral bronchitis or secondary bacterial bronchitis), cough, headache, difficulty in breathing, fatigue, dysentery, myalgia, and disseminated coagulopathy. Occasionally SARS-CoV2 infection leads to kidney failure, cardiac failure, liver damage, and uncontrolled diabetes resulting in death.[9] Recently, the COVID-19 pandemic is hitting as 2nd and 3rd waves in many countries.[10] Thus, individual clinical decisions based on the day-to-day changes in specifics of every patient are crucial during the pandemic, which may last another couple of years along with different variants *viz.*, omicron, delta, *etc.* Safety depends on vaccination and the development of effective drug molecules through repurposing and innovation.

Clinicians and researchers are doing their best to save infected individuals. Over available medications, the repurposing of drugs will be the ideal hope to save lives. Since the initial phase of the disease, clinicians and researchers have focused to repurpose the available drugs in a personalized symptom-specific manner, which essentially necessitates the quick development of new drugs. Some of the new molecules have been evaluated as potential drugs from the clinical trial done so far although most of them are still in the different phases of clinical trials.[11,12] In this comprehensive report, we aim to describe in detail the clinical advancement for repurposing of drugs for COVID-19 treatment and their pharmacological mechanism of action and briefly highlight the probable future drug targets for innovative drug development.

Repurposing of drugs for COVID-19: mode of action and clinical trial perspectives

Medical practitioners need to consider some specialized standard of care for many COVID-19 patients. To date, no effective and specific drug or antiviral agent is available for COVID-19 treatment, although some antiviral agents are currently in use. The clinical trials of some agents are in progress in multiple countries.[13] The U.S. Food and Drug Administration (FDA) has issued preliminary guidance regarding clinical trials but there remains an urgent need for clear instruction and methods to preserve the integrity of studies while enhancing patient safety during the crisis of COVID-19 treatment.[14] Clinicians and researchers are preferring repurposing drugs, the one-and-only single way to treat COVID-19. Some of the repurposed drugs are clinically approved by the drug regulatory bodies for their use. The clinical trials of a few drugs have raised conflicts and need to be verified by further clinical studies. Moreover, the repurposed drugs are still in the progressive stage of clinical studies.[15,16] The classification of these clinically tested repurposed drugs is presented in a pictorial view (Fig. 1).

Most COVID-19 patients have an aggressive course of infection and require immediate attention and prolonged durations of intensive treatment. The risk of severe COVID-19 may be increased in immunocompromised individuals with increased morbidity and mortality.[9] Additionally, many proposed measures to protect adults may not be suitable to protect children. To date, not a single drug is available in the market to specifically treat SARS-CoV-2 infection. Repurposing existing antiviral agents is a crucial platform to develop molecules for the treatment of COVID-19 patients.[17] Additionally, we are interested to highlight the clinical status of the major classes of repurposed drugs used in COVID-19 treatment and their binding details and mode of action (Table 1). Authors have also tried to provide the chemical structures of the potential repurposed drug molecules, which help researchers in the development of new structure-based drug designs against SARS-CoV-2 infection.[18,19]

Antiviral agents

Antiviral drugs are promising candidates to fight against viral diseases and may also be tested and repurposed for use in COVID-19 treatment. Currently, a number of subclasses of antiviral agents are being evaluated and repurposed to treat patients with COVID-19 *viz.*, RNA-dependent RNA polymerase inhibitors (RdRp), 5 alpha-reductase inhibitors, PDE5 inhibitors, CD147 inhibitors, protease inhibitors, RNA synthesis inhibitors, TMPRESS2 inhibitors, and some other molecules which can prevent virus attachment and several other classes of antiviral agents (Fig. 2).[17,20,21] Authors have also tried to provide the structural binding details of major drugs (Fig. 3) and their mode of action (Fig. 4).

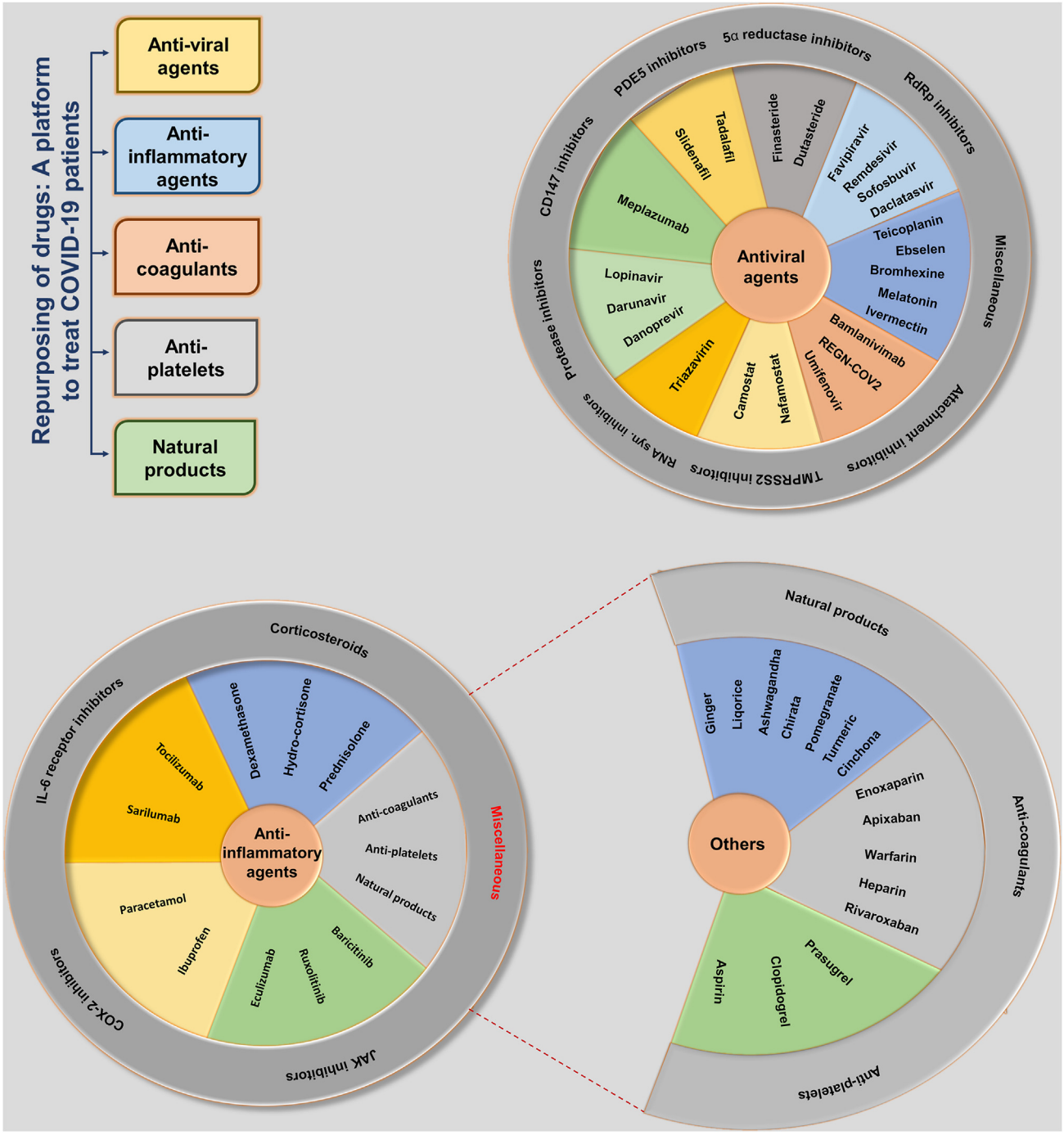

Figure 1 Pharmacological classification of potential repurposed drugs against SARS-CoV-2. **(A)** The figure represents the pharmacological classification of major potential classes of repurposed drugs; **(B)** pie chart represents the examples of various subclasses of antiviral agents; and **(C)** pie-in-pie chart represents various subclasses of anti-inflammatory agents in the left-hand side panel, and the right-hand side panel represents examples of potential anti-platelets, anti-coagulants, and natural products.

RdRp inhibitors

Remdesivir[22–24], *Favipiravir*[25–29], *Sofosbuvir*,[30–33] and *Daclatasvir*[32,34–36] — four important RdRp inhibitors under clinical evaluation for treating COVID-19 patients. The prodrug remdesivir is a nucleotide analogue that enters cells and is converted into its triphosphate form. In the human body, this form of remdesivir competes with the ATP molecules which are required for the action of RdRp complex. This remdesivir-triphosphate binds with RdRp enzyme (essential for viral RNA synthesis of SARS-CoV, MERS-CoV, and SARS-CoV-2) at ser-861 position that results in the prevention of further translocation and replication. Generally, ser-861 position is very common among alpha, beta, and delta variants of coronaviruses, suggesting that remdesivir has broad-spectrum antiviral activity.[37,38] Favipiravir is also known to bind with the catalytic domain of

Table 1 Pharmacological classification of repurposed drugs with their chemical formulas, mechanism of actions, binding sites and their efficacies.

Class of inhibitor	Drug	Chemical formula	Mechanism of action	Binding site	NCT No.	Status (Phase)	No. of enrollments	Efficacy (Method)	Reference
ANTI-VIRAL AGENTS									
RdRp	Remdesivir	$C_{27}H_{35}N_6O_8P$	⊣ translocation and replication of virus	Ser-861 of RdRp	NCT04292899	C (III)	4891	74.4% (Treated *vs* un-treated)	37, 38
	Favipiravir	$C_5H_4FN_3O_2$	⊣ viral replication	Catalytic domain of RdRp	NCT04336904	U (III)	100	Reduced viral load (Ct value)	39
	Sofosbuvir	$C_{22}H_{29}FN_3O_9P$	Terminates viral replication	NS5B and RdRp	NCT04773756	C (IV)	54	Reduced viral load (Ct value)	40, 42 43, 44
	Daclatasvir	$C_{40}H_{50}N_8O_6$	Prevents intracellular viral RNA synthesis	Hyper-phospho-NS5A					
Protease	Lopinavir	$C_{37}H_{48}N_4O_5$	⊣ protease activity o 3CLpro	$3CL^{pro}$	NCT04307693	T (II)	65	Reduced (Viral load)	66–69
	Darunavir	$C_{27}H_{37}N_3O_7S$	⊣ protease dimerization	—	NCT04252274	U (III)	30	(Reduced symptoms)	70–72
	Danoprevir	$C_{35}H_{46}FN_5O_9S$	⊣ viral protease activity	—	NCT04345276	C (IV)	10	Symptom improved	92, 93
CD147	Meplazumab	—	⊣ entry of SARS-CoV-2	S protein	NCT04586153	R (II/III)	456	Improved (Ab titre)	95–98
TMPRSS2	Nafamostat	$C_{19}H_{17}N_5O_2$	⊣ penetration of SARS-CoV-2	TMPRSS2	NCT04483960	R (III)	2400	Inhibition of entry (Mortality)	137
	Camostat	$C_{20}H_{22}N_4O_5$	⊣ penetration of SARS-CoV-2	TMPRSS2	NCT04583592	C (II)	295	Reduced disease progression	137
RNA synthesis	Triazavirin	$C_5H_7N_6NaO_5S$	Broad-spectrum antiviral agent	E, S, CL_{pro} and ACE-2	NCT04973462	R (IV)	80	Improved recovery (PCR)	104–106
Viral attachment	Umifenovir	$C_{22}H_{25}BrN_2O_3S$	⊣ viral attachment to host cells	RBD & ACE-2	NCT04350684	U (IV)	40	Improved (Mortality)	138–140
	Bamlanivimab	—	Recombinant mAb	Spike proteins	NCT04656691	T (IV)	139	Side-effects	122–124
	HCQ/CQ	$C_{18}H_{26}ClN_3O$	↓PG's synthesis, ↓IL-1 level and ↓superoxide production	—	NCT04342221	T (III)	30	Reduced viral load (PCR)	126, 127
	REGN-COV2	—	mAb	RBD	NCT05502081	C (IV)	265	Improved (Ab titre)	116–118
PDE5	Slidenafil Tadalafil	$C_{22}H_{30}N_6O_4S$ $C_{22}H_{19}N_3O_4$	↓PDE5 enzyme ↑cGMP level	—	—	—	—	—	144, 145
5α reductase	Finasteride Dutasteride	$C_{23}H_{36}N_2O_2$ $C_{27}H_{30}F_6N_2O_2$	↓5-alpha-reductase	—	NCT04729491	C (II/III)	138	Reduced viral load (PCR)	152–158
ANTI-INFLAMMATORY AGENTS									
Cortico-steroids	Dexamethasone HydrocortisoneMethyl-prednisolone	$C_{22}H_{29}FO_5$ $C_{22}H_{30}O_8S$ $C_{22}H_{30}O_5$	↓Transcription of pro-inflammatory mediators (*viz.*, cytokines, adhesion molecules and chemokines) ↑Transcription of anti-inflammatory cytokines	M_{pro} — —	NCT04866082	R (—)	1000	Reduced symptoms (Mortality)	191–194
IL-6 receptor	Tocilizumab Sarilumab	—	mAbs; ⊣	IL-6R	NCT04386239/ NCT05017441	R (I)/ R (—)	40/1200	Improved respiratory functions	204

(*continued on next page*)

Table 1 (*continued*)

Class of inhibitor	Drug	Chemical formula	Mechanism of action	Binding site	NCT No.	Status (Phase)	No. of enrollments	Efficacy (Method)	Reference
			IL-6 receptor mediated signaling						
COX-2	Paracetamol Ibuprofen	$C_8H_9NO_2$ $C_{13}H_{18}O_2$	⊣	— M_{pro}	—/NCT04500639	—/A (—)	—/461	Reduced fever	207, 208
			COX-2 signaling cascade						
JAK	Baricitinib	$C_{16}H_{17}N_7O_2S$	↓Cytokine storm	—	NCT04421027	C (III)	1525	Reduced symptoms (Mortality)	212
			⊣						
			viral assembly						
	Ruxolitinib	$C_{17}H_{18}N_6$	⊣	—	NCT04377620	T (III)	211	More deaths (Mortality)	217
			JAK1 and JAK2						
	Eculizumab	—	mAb	Terminal complement C5	NCT04346797	U (II)	120	—	220
ANTI-PLATELETS									
	Clopidogrel Prasugrel	$C_{16}H_{16}ClNO_2S$ $C_{20}H_{20}FNO_3S$	Antagonists of $P2Y_{12}$ receptor	—	NCT04409834/ NCT04445623	C (IV)/U (III)	390/128	Improved venous thromboembolism	222
	Aspirin	$C_9H_8O_4$	⊣	—	NCT04768179	NR (II/III)	490	Improved respiratory functions	221
			thrombo-inflammation						
ANTI-COAGULANTS									
	Heparin Warfarin	$C_{12}H_{19}NO_{20}S_3$	Neutralizes cytokines and	RBD	—	—	—	Prevented coagulation	239—249
	Apixaban Enoxaparin	$C_{19}H_{16}O_4$	chemokines,	—					
	Rivaroxaban	$C_{25}H_{25}N_5O_4$	⊣	M_{pro}					
		$C_{26}H_{42}N_2O_{37}S_5$		—					
		$C_{19}H_{18}ClN_3O_5S$	heparanase, neutralizes	—					
			extracellular cytotoxic histones,						
			⊣						
			leukocyte trafficking and viral entry						

Abbreviations: RdRp: RNA dependent RNA polymerase; NS5B: non-structural protein 5B; $3CL^{pro}$: 3-chymotrypsin-like protease; S: Spike proteins; E: Envelope; TMPRSS2: Transmembrane serine protease-2; ACE-2: Angiotensin converting enzyme-2; RBD: Receptor binding domain; M_{pro}: Main protease; COX-2: Cyclo-oxygenase-2; IL-6R: Interleukin-6 receptor; PDE5: Phospho-di-esterase type 5; PG's: Prostaglandins; HCQ/CQ: Hydroxychloroquine/chloroquine; cGMP: Cyclic guanosine monophosphate; C: Completed; T: Terminated; NR: Not Recruiting; A: Active and U: Unknown. Arrows ⊣, ↑ and ↓ indicates inhibition, increase and decrease respectively.

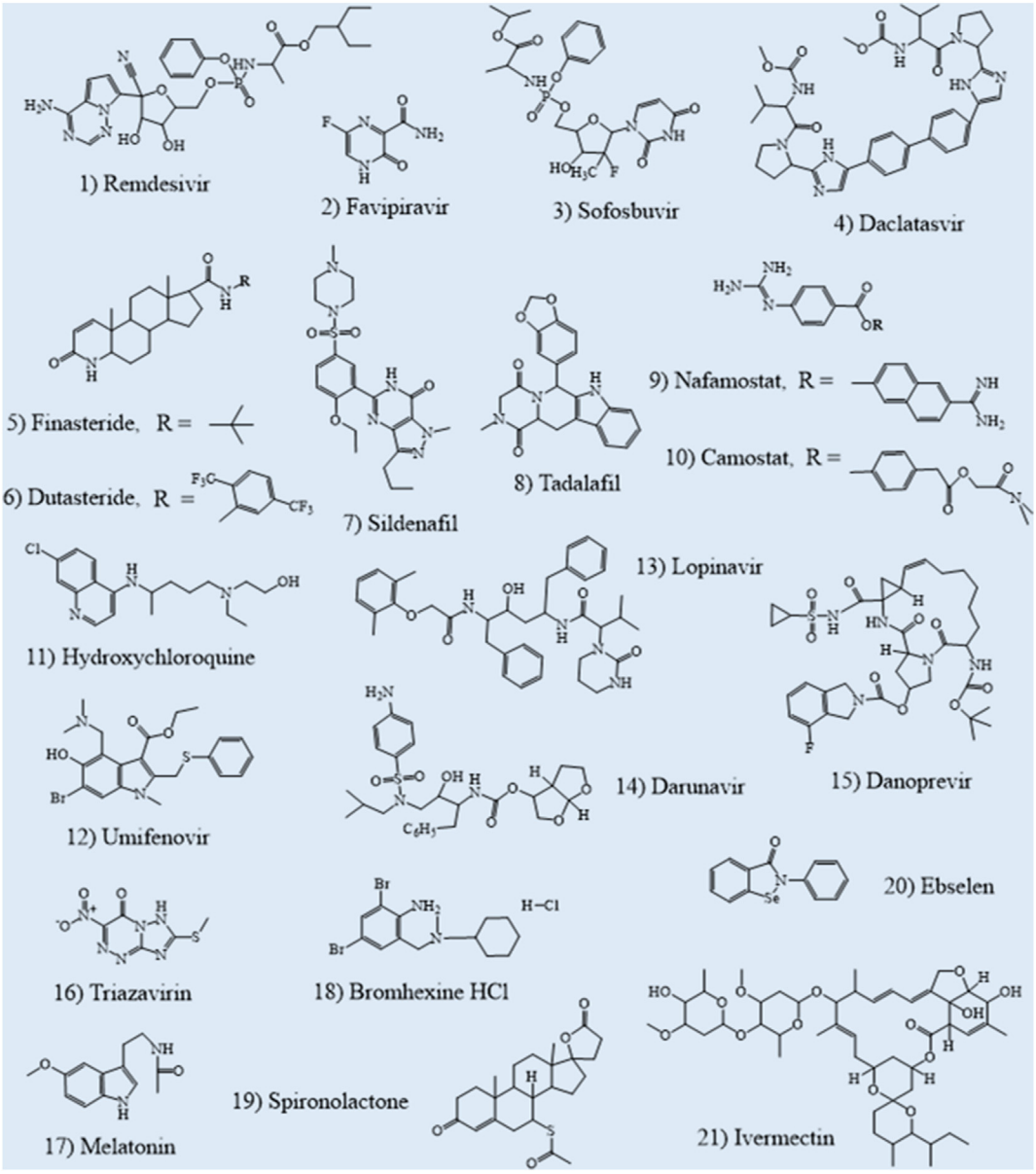

Figure 2 Chemical structures of repurposed antiviral drugs. The figure depicts the chemical structures of various sub-classes of antiviral agents such as RdRp inhibitors (remdesivir, favipiravir, sofosbuvir, and daclatasvir), 5-alpha reductase inhibitors (finasteride and dutasteride), PDE5 inhibitors (sildenafil and tadalafil), TMPRSS2 inhibitors (nafamostat and camostat), viral attachment inhibitors (umifenovir and hydroxychloroquine), protease inhibitors (lopinavir, darunavir, and danoprevir), RNA synthesis inhibitors (triazavirin), and miscellaneous antiviral agents (melatonin, ebselen, spironolactone, bromhexine HCl, and ivermectin). All the structures were drawn using chem-draw software.

RdRp enzyme and results in the prevention of viral replication. The catalytic domain of RdRp is conserved in most RNA viruses, which suggests that favipiravir also has a broad antiviral spectrum.[39] Similarly, sofosbuvir acts by binding to the NS5B (non-structural protein 5B) and RdRp, which results in the termination of any further viral replication.[40—42] Similarly, daclatasvir targets the hyper-phosphorylated form of NS5A (a viral non-structural phospho-protein) and results in the prevention of intracellular viral RNA synthesis.[43,44] Taken together, all these drugs targeting the RdRp enzyme finally result in the termination or prevention of viral replication.

Several reports related to the clinical perspectives of remdesivir effectiveness in COVID-19 were recently generated. A group has reported no significant clinical improvement for patients treated with remdesivir when compared with placebo groups in a randomized clinical trial of placebo-controlled and in a double-blind study conducted in COVID-19-positive hospitalized adults.[45] Another group has also found no significant clinical difference in comparison to standardized hospital care after the 10-day course of remdesivir treatment against moderate COVID-19 pneumonia and severe acute respiratory syndromes in COVID-19 patients. Interestingly, they also found that patients

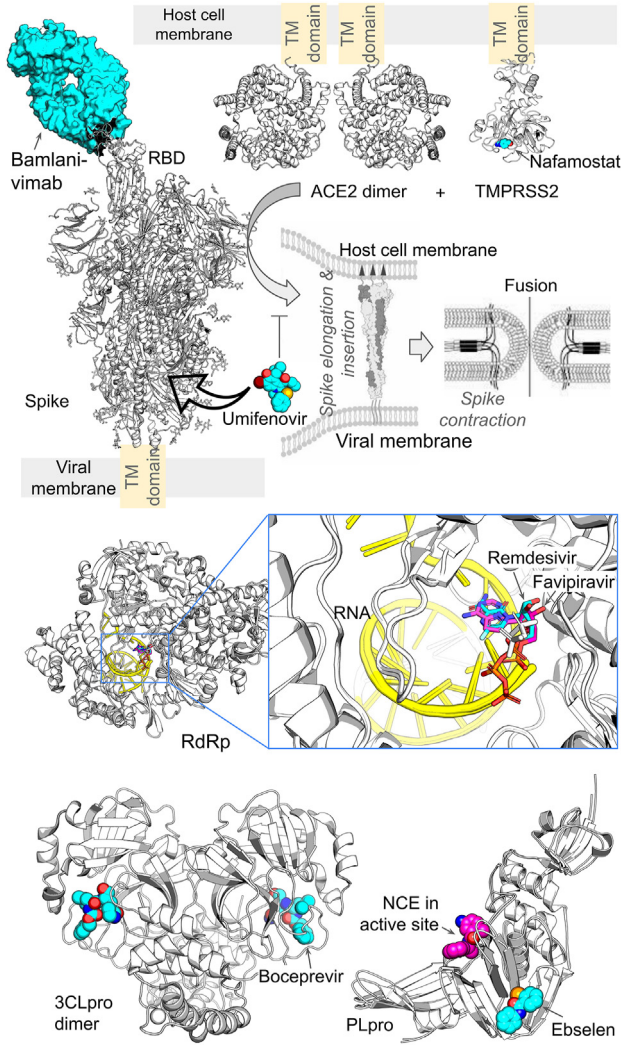

Figure 3 Structural details of viral/host target with drug binding site. Top panel: Entry inhibition by targeting viral spike protein with monoclonal antibody bamlanivimab (PDB: 7kmg). It binds to the receptor-binding domain (RBD) of spike protein and thus prevents its interaction with the ACE2. Umifenovir potentially binds to the stem region of spike protein causing conformational lock and thus preventing fusion (similar to PDB: 5t6s). Nefamostate binding to the TMPRSS3 extracellular domain inhibits its action (PDB: 7meq). Middle panel: Inhibition of viral replication by chain terminators. Remdesivir and favipiravir are incorporated into the growing RNA chain by RdRp, which eventually leads to the blockage of viral replication (PDB: 7aap and 7bv2). Bottom panel: Protease inhibitors bind to the catalytic site and inhibit the function of major protease 3CLpro (PDB: 6wtt). Protease inhibitors can also target the catalytic or allosteric site of the viral papain-like protease PLpro and inhibit its action (PDB: 7m1y and 7cjm).

treated with a 5-day course of remdesivir had a significant change in clinical status, but that amount of change is not significant for clinical importance.[46] Furthermore, another group (NIAID-ACTT-1) has found a reduction in the recovery time of hospitalized adult patients with COVID-19 in a placebo-controlled, randomized and double-blind study. COVID-19 patients receiving remdesivir had 10 days of median recovery time while placebo-receiving COVID-19 patients had 15 days of median recovery time.[47] Based upon these NIAID-ACTT-1 trial by European Medicines Agency (EMA) has approved the remdesivir conditional marketing to use in adults and adolescents above 12 years who tested positive for COVID-19 and require oxygen care.[48] Remdesivir is the first medicine recommended in Europe for COVID-19.[49,50] Finally on November 20, 2020, WHO recommended the use of remdesivir in hospitalized COVID-19 patients.[51,52]

Several clinical studies have been performed to study the safety and efficacy of remdesivir in COVID-19 patients. They suggest no such severe side effects related to the kidney and liver with the administration of 3—225 mg remdesivir. It is approved by the FDA in Japan, Canada, and other European countries. However, several mild-to-moderate side effects such as renal impairment, rashes, diarrhea, increment in hepatic enzymes, and hypotension have been observed in treated COVID-19 patients. Also, a few patients with severe side effects such as septic shock, multiple-organ dysfunction syndrome, hypotension, and acute kidney injury are observed in 12 patients. To further solidify its safety and efficacy, many studies are needed to be performed on many patients and needed to be performed on children and breastfeeding females.[48,49]

Favipiravir — approved in Japan and known to treat viral influenza.[53,54] In a purpose to collect evidence of favipiravir clinical safety and efficacy in comparison with umifenovir in COVID-19 treatment, a randomized clinical trial was performed. It was found that favipiravir has higher efficacy than umifenovir although has some serious side effects *viz.*, elevation in uric acid level, abnormal GIT symptoms, abnormality in liver enzymes, and psychotropic side effects.[55] Further, favipiravir in combination with IFN-α aerosol inhalation in COVID-19 was evaluated in another open-label clinical study, which showed better chest computed tomography (CT) image and rapid viral clearance in comparison with only favipiravir-treated control patients.[56,57] In contrast, a few opposite results were also reported in clinical studies of favipiravir *viz.*, in combination with IFN-β-1b inhalation, which showed no such significant difference in inflammatory biological markers.[56,58] The opposing evidence for the virological effectiveness of favipiravir was also reported, but along with this authors have also concluded that these results were produced due to its insufficient concentration enrichment for the antiviral activity.[59] Further, in another multicentric phase II/III clinical trial favipiravir is documented as a faster and more effective antiviral agent in comparison to standard hospital care of COVID-19 patients.[60] After the review of the preliminary clinical evidence, the Russian Ministry of Health authorized favipiravir to treat COVID-19 patients.[60,61] At present, two clinical trials NCT04310228[62] and NCT04336904[63] of favipiravir are ongoing.

Out of five trials, one clinical study is studied to have a significant reduction in viral load. Reduction in Ct value and viral replication, and improvement in chest imaging and symptoms are the advantages of these clinical studies. Lower sample size, sampling from specific origin populations, lesser studies, and several adverse events are the main disadvantages of these studies. To clarify and solidify these results many studies are needed to be performed globally in many patient groups.[62,63]

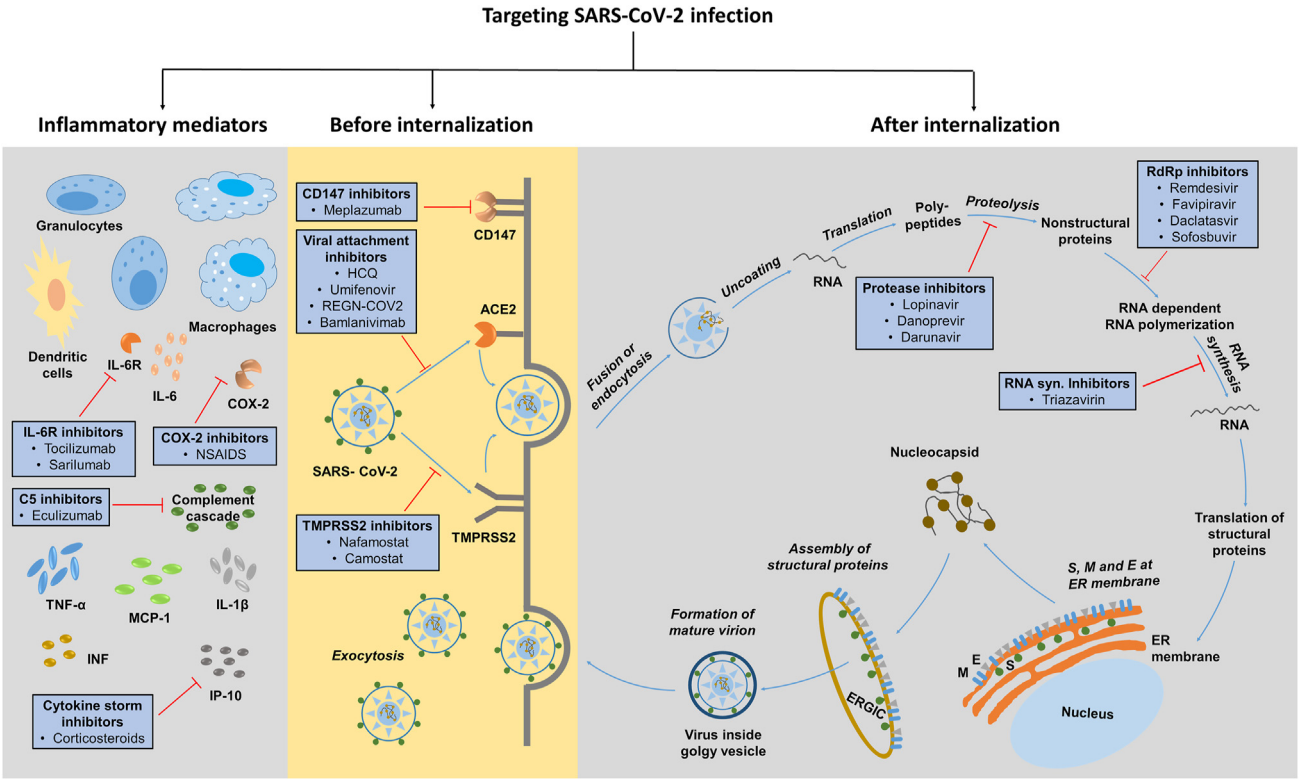

Figure 4 Mechanism of actions (MOAs) of clinically tested drugs to target SARS-CoV-2 infection. The figure depicts the MOAs of various drugs in three compartments (*viz.*, inflammatory mediators, and viral pre- and post-internalization targeting).

Sofosbuvir and Daclatasvir — RdRp inhibitors have been clinically evaluated in several COVID-19 patients. To examine the clinical effectiveness along with standard patient hospital care, a randomized clinical trial was performed with a combination of sofosbuvir and daclatasvir, which showed that patients under treatment along with standard hospital care gets recovered much faster than only standard hospital care.[35,64,65] Still, sofosbuvir and daclatasvir have not been approved yet by any authority for their clinical use in COVID-19 patients.

Protease inhibitors

Lopinavir — a protease inhibitor previously used in a combination with ritonavir against HIV-1 and HIV-2 infections. In a combination treatment, ritonavir (cytochrome P450 inhibitor), enhances the lopinavir's plasma concentration. 3-Chymotrypsin-like protease ($3CL^{pro}$) is responsible for the processing of viral RNA. Furthermore, lopinavir is effective to inhibit the protease activity of $3CL^{pro}$, resulting in the inhibition of viral replication.[66–69] Furthermore, darunavir, a protease dimerization inhibitor, can also prevent viral replication.[70–72] It is mostly preferred in combination with cobicistat, another cytochrome P450 inhibitor that helps increase the plasma concentration of darunavir.[73–75] Still, the exact role and effectiveness of danoprevir and darunavir are not studied yet in detail.

Lopinavir and *Ritonavir combination* — To determine the effectiveness of lopinavir and ritonavir combination treatment, a randomized clinical trial was performed in COVID-19 hospitalized patients; results showed no such significant difference in patient's clinical status in comparison to standard hospital care alone.[76–80] In addition, this combination did not show any reduction in hospital stay, 28 days of mortality rate, duration of mechanical ventilation, or risk of death.[81] Two types of meta-analysis were also conducted further to see the difference in efficacy of lopinavir and ritonavir combination therapy. In the first case, patients treated with a combination of lopinavir and ritonavir were compared with either umifenovir or hydroxychloroquine (HCQ) treated patients[82] while in the second case, it was compared with standard hospital care patients with negative RT-PCR report.[83] In both studies, no significant difference was observed in terms of efficacy.[82,83] Next, an interesting retrospective cohort clinical study was further performed on COVID-19 patients, to study the difference in efficacy of a triple combination including lopinavir, ritonavir, and umifenovir in comparison to a double combination of lopinavir and ritonavir. It was found that triple combination is much more efficacious than double combination or monotherapy.[84,85] However, daily use of lopinavir or ritonavir by COVID-19 patients is not preferred.[86,87] Hence, based on all these clinical reports, more careful studies needed to be performed to sort out their effectiveness.

A total of seven clinical studies were performed to determine the efficacy and safety of the lopinavir and ritonavir combination. Two out of the seven clinical studies (*viz.*, TOGETHER and RECOVERY) were found to significantly inhibit the protease and reduce the viral load which is the main advantage of these studies. These are performed in a lesser number of patients which is one of the major

limitations. Kaletra administration improves potassium and albumin levels, eosinophil count, and lymphocyte level in treated patients. Improvement in eosinophil count is a significant marker in the recovery from COVID-19. To improve and solidify these results, a larger number of clinical trials in a large number of patients needed to be performed.[84–86]

Darunavir and *Cobicistat* combination — previously used this combination against the HIV-1 infection.[75,88] The use of darunavir against SARS-CoV-2 viral replication is not clear; lots of conflicts still exist.[89] To study the clinical importance of darunavir, a comparison between cobicistat and IFN-α-2b combination and IFN alpha-2b alone in COVID-19 treatment was performed; no such significant difference in the mortality rate and no difference in the RT-PCR report on day seven was observed.[90] Recently another report showed an opposing effect indicating that the use of darunavir and cobicistat combination reduces the COVID-19 mortality rate in COVID-19 patients with critical illness.[91] However, the effect of darunavir and cobicistat combination against SARS-CoV2 infection is not that much clear, so further clinical trials are needed.

Danoprevir — a macrocyclic peptidomimetic inhibitor used before against a protease of hepatitis-C virus.[92] In an open-label clinical trial, danoprevir in combination with ritonavir is evaluated as an effective treatment for COVID-19.[93] In a phase-II clinical trial, the danoprevir and ritonavir combination proves much more effective than the lopinavir and ritonavir combination. A Chinese manufacturer (Ascletis Pharma Inc.) in a phase-IV clinical trial evaluated the danoprevir and ritonavir combination with or without interferon inhalation and reported faster recovery from pneumonia of COVID-19 patients.[94]

CD147 inhibitor

Meplazumab — CD147 is a glycoprotein that helps the entry of SARS-CoV-2 virus by associating with coronavirus S protein.[95,96] It also has a pro-inflammatory activity that regulates leukocyte recruitment and cytokine secretion in viral infections.[96,97] Monoclonal antibody meplazumab is a CD147 inhibitor that causes inhibition of SARS-CoV-2 virus entry. In a preliminary study, meplazumab was found to be effective against pneumonia in COVID-19 patients.[98] To assess further the efficacy and safety of meplazumab in COVID-19 treatment, two clinical trials are in process with registered numbers NCT04275245[99] and NCT04586153.[100] These clinical trials may indicate a new hope to the world.

TMPRSS2 inhibitors

Nafamostat and *Camostat* — TMPRSS2 is a protease that helps in the penetration of SARS-CoV-2 virus into the host cell. Nafamostat and camostat are two TMPRSS2 inhibitors found to be clinically effective in the inhibition of TMPRSS2-mediated penetration of SARS-CoV-2.[101] In the preliminary studies, a combination of nafamostat with either favipiravir or HCQ was found to be more effective in severe COVID-19 patients.[101,102] Furthermore, nafamostat is also found to be an effective agent against pneumonia in COVID-19-positive older patients.[103] Along with these few clinical trial results, more clinical studies needed to be done to investigate any adverse effects concerning oxygen support, viral clearance, and mortality rate of COVID-19 patients.

RNA synthesis inhibitors

Triazavirin (Riamilovir) — is a broad-spectrum antiviral drug that inhibits viral RNA synthesis. It was primarily developed against the H5N1 strain of influenza.[104–106] Previously it was used for anti-influenza and treatment against numerous viruses *viz.*, forest spring encephalitis,[107] tick-borne encephalitis,[105] ebola,[108] and Lassa fever.[108] Recently, triazavirin is tested and evaluated against COVID-19 in South Africa, China, and Russia. The Russian Ministry of Health approved triazavirin for COVID-19 treatment through oral routes.[109–113] In another preclinical study, aerosol inhalation delivery of triazavirin in mice showed improvement in bioavailability and effectiveness than oral administration.[114] Further, a pilot randomized controlled trial of triazavirin was performed and reported no such significant change in clinical improvement in comparison to the placebo group. One more study was conducted in Heilongjiang Province, China on 240 COVID-19 participants. This study showed that the condition of triazavirin group patients was improved compared with the control group. Hence this study is contradictory to the previous studies, showing a new hope for clinicians.[111] Currently, a clinical study registered with trial no. NCT04581915 for evaluation of the safety and efficacy of triazavirin against mild to moderate SARS-CoV-2 infection is ongoing.[115]

Viral attachment inhibitors

REGN-COV2 — It is a combination of two monoclonal antibodies *viz.*, imdevimab and casirivimab.[116] In preliminary clinical studies, *REGN-COV2* is reported to reduce the time of symptomatic relief and viral load in non-hospitalized COVID-19 patients.[117] Regeneron Pharmaceuticals, Inc. also showed a reduction in the hospital visiting frequency of home quarantine COVID-19 patients after the use of *REGN-COV2* antibody cocktail.[118] After a review of its effectiveness, on November 21, 2020, US Food and Drug Administration (US-FDA) approved its emergency use in mild or even moderate to severe COVID-19 patients aged 12 or more with a body weight of at least 40 kg.[116] For evaluation of the safety and efficacy of this monoclonal antibody cocktail in COVID-19 patients, currently, four clinical trials are ongoing *viz.*, NCT04425629,[119,120] NCT04426695,[119] NCT04381936[121] and NCT04452318 for a clear understanding of its adverse effects, cross-reactivity, and effect on mortality rate.[120]

Bamlanivimab — a human recombinant monoclonal antibody, designed against the SARS-CoV-2 spike proteins. Phase-I clinical trial was performed by Eli Lilly company in hospitalized patients,[122] while the phase-II clinical trial was conducted by BLAZE-1 in non-hospitalized patients.[123,124] After a review of results obtained from these clinical trials, on November 9, 2020, FDA approved and recommended its use in an emergency immediately after getting a COVID-19 positive report or within 10 days of the onset of symptoms.[116] Currently, the phase-III clinical trial of bamlanivimab is ongoing to assess its effectiveness in the prevention of COVID-19.[125]

Hydroxychloroquine (HCQ) and *chloroquine* (CQ) — the molecules with significant importance reported in few clinical studies for their effectiveness against COVID-19. Previously, these drugs are known for the treatment of malaria and several rheumatic diseases.[126] These drugs

show several effects *viz.*, inhibition of prostaglandins synthesis, recruitment of polymorphonuclear bodies and phagocytosis, inhibition of IL-1 production by monocytes, and inhibition of superoxide release by neutrophils.[127] Recently, these drugs are also documented to prevent the replication of SARS-CoV-2 in experimental models. To evaluate the safety and efficacy of HCQ, several clinical trials were performed. HCQ in combination with azithromycin was used in 36 hospitalized COVID-19 patients in a single-arm interventional study and showed its effectiveness on the 6th day of treatment by reducing the viral load in comparison to control groups.[128–130] Another study related to HCQ and azithromycin combination found no reduction in viral load after 5–6 days of administration. This study was performed in a group of 11 hospitalized COVID-19 patients. The opposing results create a lot of conflicts about the effectiveness of this combination.[131] Another study also reported no reduction in viral load in comparison to standard hospital care.[91] In support of these opposing results, further study was performed and showed no change in the severity of symptoms after the use of HCQ for 14 days in a group of 491 early-stage COVID-19 patients.[132] Furthermore, a randomized clinical study states that by day 14, 100% of HCQ-treated patients were discharged from the hospital in comparison to 50% who use lopinavir or ritonavir.[133] As HCQ is reported to produce disturbances in cardiac rhythms.[134] EMA drew attention and allowed the prescribers to use this drug for hospitalized patients only in emergency conditions under close monitoring due to some confusion that is persisting even after the publication of several reports related to safety and efficacy.[134,135] Next, US FDA also approved a similar type of guideline for the use of HCQ. After all these trials, WHO suspended the multicentric clinical trials of HCQ in June 2020 because EMA has reported multiple side effects of this drug including suicidal behavior and psychotropic disorders.[136] The safety and efficacy of these antimalarial drugs are still not fully understood.

Chloroquine use in combination with macrolide antibiotic is reported to have serious cardiac side effects (*viz.*, cardiac hypertrophy, congenital heart failure, and tachycardia). HCQ-receiving COVID-19 patients with other diseases (*viz.*, diabetes, obesity, and heart diseases) are clinically studied with serious complications. Based upon this knowledge, HCQ is not further prescribed for COVID-19 treatment. A total of 23 clinical studies were conducted to evaluate the safety and efficacy of HCQ in COVID-19 patients and its use is contraindicated in these co-morbidity cases. Overall, the consumption of 600 mg HCQ is clinically tested to have 70% efficacy in COVID-19 patients. These studies are still needed to be re-evaluated in a large sample size.[134–136]

Umifenovir (Arbidol) — an indole derivative that has profound efficacy against influenza and hepatitis C virus by inhibiting the virus attachment to the host.[137] Umifenovir is preferred to administer three times a day but not more than 10 days.[138] Preliminary studies with umifenovir were reported to inhibit SARS-CoV-2 infections at a dose of 10–30 μM. It prevents infections in a group of umifenovir-treated healthcare workers as compared to the untreated group.[139] Recently, another study has shown the synergistic effect of umifenovir in combination with antiviral agents.[140] Based on these preliminary results, a recent study was done and showed the clinical effectiveness of umifenovir in combination with lopinavir or ritonavir in COVID-19 treatment. This small-scale clinical trial showed a prominent reduction in mortality rate and effectiveness.[85] Furthermore, another clinical trial of HCQ in combination with umifenovir/Kaletra was performed by the Iran University of Medical Sciences (Trial registration, IRCT20180725040596N2, 18 April 2020). This study concludes HCQ in combination with umifenovir is much more effective than the use of only Kaletra. However, such a study in a group with a larger population is needed to be done for a better understanding.[141] Currently, the phase-IV clinical trial (NCT04350684[142]) is ongoing to investigate its effectiveness and effects on mortality rate, ventilation status, and adverse side effects.

A limited number of clinical studies with the use of arbidol have been performed in COVID-19-infected patients. It is found effective against this infection but still, there is confusion regarding this. It is very difficult to identify whether the patients have been cured with natural immunity or via medications. Thus, a lot of focused work is needed to be done in this regard.[141,142]

PDE5 inhibitors

Sildenafil and Tadalafil — PDE5 (phosphodiesterase-5) inhibitors that pharmacologically indirectly belong to the antiviral class of drugs. These drugs act by inhibiting the PDE5 enzyme and cause an increase in cyclic GMP level and finally give rise to smooth muscle relaxation.[143] These drugs are mostly used to treat erectile dysfunction and have recently been evaluated to use in pulmonary fibrosis and arterial hypertension.[144] Sildenafil is evaluated to block and prevent the progression of pulmonary fibrosis and will help in the improvement of respiration in COVID-19 patients. Thus these drugs are capable of improving the respiration problems of COVID-19 patients after the inhibition of PDE5 and thus causing the inhibition of pulmonary fibrosis.[145–148] Currently, a phase-III clinical trial registered with trial no. NCT04304313 in COVID-19 patients is ongoing.[149] On the other hand, tadalafil is reported to selectively inhibit the PDE5 activity with an IC_{50} of 5 nM, while sildenafil can inhibit both PDE5 and PDE6 with an equal potential.[150] Tadalafil dose is preferred to be used once a day to treat erectile dysfunction in COVID-19-recovered patients who are not interested in sexual activity.[145]

5-alpha reductase inhibitors

Dutasteride and *Finasteride* — two important 5-alpha reductase inhibitors. The enzyme 5-alpha-reductase helps in the conversion of testosterone into di-hydro testosterone and promotes the expression of transmembrane protease, serine 2 (TMPRSS2). TMPRSS2 has a major role in the penetration of SARS-CoV-2 virus into the host cells.[151] Dutasteride and finasteride are used in clinical practice against SARS-CoV-2 infections. These drugs reduce the expression of TMPRSS2 and cause the prevention of SARS-CoV-2 virus penetration and replication.[152–157] It was also found that TMPRSS2 expression is much higher in men than in women. Based on this fact, the testing for these drugs found that COVID-19-positive hospitalized men require very less intensive care unit (ICU) admission in comparison to

control groups. This may be a preventive major in early COVID-19 patients to reduce the severity and casualties.[158,159] Currently, an ongoing clinical trial of dutasteride against SARS-CoV-2 infections is continuing (trial number NCT04446429, approved by Brazilian National Ethics Committee).[160]

Miscellaneous antiviral agents

Ebselen, Statins, Spironolactone, Bromohexine HCL, Melatonin, Teicoplanin, and *Ivermectin* —miscellaneous molecular agents being evaluated against SARS-CoV-2 infection. Ebselen is previously known to use against HIV-1,[161] zika virus,[162] hepatitis c virus,[163] and influenza-A virus.[164] Liver injury is the major problem observed in severe COVID-19 patients.[165] It is reported to prevent liver injury.[166,167] Further, ebselen also shows its effectiveness in focal ischemic injury by decreasing interleukin-6 (IL-6) levels. Through this mechanism, there may be a new hope for managing SARS-CoV-2 infection.[168,169] It also has antiviral activity against SARS-CoV-2 infections via inhibition of Mpro.[166,170] Furthermore, the natural hormone melatonin is secreted from the pineal gland which regulates the sleep cycle. Along with this, it has antioxidant property that helps reduce the reactive oxygen species (ROS) generated in COVID-19 patients. Additionally, it decreases the cytokine storm that leads to the reduction in the mortality rate in COVID-19.[171–173]

Statins — known for their anti-inflammatory effect. COVID-19 patients with severe illness and high IL-6 levels were treated with several anti-inflammatory agents such as statins.[174–176]

Spironolactone — known as an anti-hypertensive and anti-androgenic agent. It is a potassium-sparing diuretic that acts in the reticular activating system by reducing ACE2 receptor expression due to its anti-mineralocorticoid activity. It is also found to reduce the TMPRSS2 expression due to its anti-androgenic activity. Thus, repurposing spironolactone may be a new hope for clinicians and COVID-19 patients.[177,178]

Bromhexine-HCL — known as an effective expectorant in wet cough. Few studies have shown that its use in COVID-19 patients reduces the TMPRSS2 expression level that results in the inhibition of the penetration of SARS-CoV-2 virus to the host. Thus, this may be an effective molecule against COVID-19.[179–182]

Teicoplanin — a glycopeptide antibiotic, reported against SARS-CoV-2 infections. Previously, it is known to be effective against HIV, ebola, SARS, MERS, and influenza viruses.[183,184] It inhibits viral replication. It acts in the early stage of the virus life cycle by cleaving the viral spike proteins due to low pH.[185]

Ivermectin — is tested and evaluated for SARS-CoV-2 infections. It is a broad-spectrum antiviral agent which acts against both RNA and DNA viruses. Importin α/β helps in the nuclear transport of HIV-1 integrase, NS5 polymerase, NS3 helicase, and UL42. The antiviral activity of ivermectin may attribute to the prevention of nuclear import of important viral components due to the inhibition of importin α/β.[186,187] Thus, the action of ivermectin is a new hope to clinicians for COVID-19 treatment.[188,189]

In vitro studies have shown its 5000-fold virus inhibitory potential in Vero/hSLAM cells at a dose of 5 uM concentration in 48 h. In multiple drug combinations, it is also observed to have no such serious adverse effects in treated individuals. The combination of ivermectin and doxycycline is also observed to lower viral clearance in COVID-19 patients. To date, a very small number of *in vivo* studies have been performed, so it is necessary to explore this area.[186,187]

The abovementioned antiviral agents are the first line of choice of antiviral drugs against SARS-CoV-2 infections, but other classes of drugs like anti-inflammatory drugs, anti-platelets, anti-coagulants, and even traditional natural products are also being evaluated against SARS-CoV-2 infections. Thus, in the next few sections, we are interested to discuss other classes of drugs repurposed for COVID-19 treatment.

Anti-inflammatory agents

A few anti-inflammatory drugs are also eminent candidates and can be used to provide symptomatic relief for COVID-19 patients. Currently, a few sub-classes of anti-inflammatory agents are being evaluated and repurposed for COVID-19 *viz.*, corticosteroids, IL-6 receptor inhibitors, COX-2 inhibitors, and JAK inhibitors (Figs. 5 and 6). We are interested to discuss the clinical evidence of individual and combination treatment of the anti-inflammatory molecules followed by anti-platelet, anti-coagulants, and natural product-based molecules, and their mode of action (Fig. 4). Authors have also tried to provide the structural binding details of drug molecules with host cell proteins for alleviating the symptoms of SARS-CoV-2.

Corticosteroids

Dexamethasone, *Methylprednisolone*, and *Hydrocortisone* — the three mostly used corticosteroids for symptomatic relief and prevention of the worse effects of severe COVID-19. Corticosteroids act as anti-inflammatory agents basically through two possible mechanisms of action *viz.*, (i) reduction in the transcription of pro-inflammatory mediators (*viz.*, cytokines, adhesion molecules, and chemokines) and (ii) increase in the transcription of anti-inflammatory cytokines. These two possible mechanisms of corticosteroids result in the inhibition of cytokine storm, an important characteristic feature of COVID-19. The preliminary results for the use of dexamethasone in COVID-19 provide strong evidence for its effectiveness. In a randomized, open-label, controlled study, patients are divided into two groups; the first group ($n = 2104$) was treated with an oral or intravenous 10 mg/day dose and followed up to 10 days, while the second group ($n = 4321$) received the usual hospital care alone. This study found the group treated with dexamethasone (with or without mechanical ventilation) showed a reduction in mortality rate and the chance of respiration failure in contrast with the control group.[190–193] Few more randomized clinical trials have reproduced the same results; thus, dexamethasone could be a prominent drug candidate for the treatment of severe COVID-19 patients who even requires respiratory support. Based on all these preliminary results, EMA has approved the dexamethasone use with a dose of 6 mg/day in adults and adolescents and continued up to 10 days in severe

COVID-19 patients.[194–196] Recently, WHO has performed a meta-analysis of seven randomized clinical trials and analyzed the efficacy of dexamethasone, hydrocortisone, and methylprednisolone in a group of 1703 COVID-19 hospitalized patients. This study showed that the reduction in mortality rate occurs after the administration of corticosteroids.[197] Contrary to their effectiveness in COVID-19 patients, cases of mucormycotic or black fungus have been found in recovered patients. Dr. Rommel Tickoo (Director of Internal Medicine at Max Hospital, New Delhi, India)[198] and Director of AIIMS hospital, New Delhi, India had explained the reason for black fungus.[199] Black fungus cases are mostly found in COVID-19-recovering patients who are treated with an overdose of corticosteroids. They explained that black fungus cases were found mostly in immune-compromised patients (*viz.*, cancer, diabetes, *etc.*) with COVID-19, and patients who are treated with steroidal drugs for the cure of COVID-19. Along with this, they explained the overdose of corticosteroids causing black fungus infection in COVID-19 recovering patients.[198,199] To date, no clinical report is published related to black fungus due to corticosteroids. Moreover, an antifungal drug amphotericin-B is used to treat this black fungus infection.[200] So, more attention and research are needed to be done for the use of corticosteroids in COVID-19 patients. Currently, two clinical trials NCT00294684[201] and NCT04273321[202] of corticosteroids are ongoing for determination of their safety and efficacy.

After multiple clinical applications and studies, its use is still controversial in COVID-19 treatment. It is only preferred for its anti-inflammatory property and for treating acute respiratory problems caused by SARS-CoV-2 infection. Current evidence showed only symptomatic relief in COVID-19 patients but no reduction in viral load.[201,202]

IL-6 receptor inhibitors

Tocilizumab and *sarilumab* — two monoclonal antibodies used in COVID-19 treatment for inhibition of IL-6 receptor-mediated signaling. Recently, one study was performed to evaluate the sarilumab efficacy in a group of eight hospitalized COVID-19 older patients. In this study, 400 mg of sarilumab in combination with any of the agents *viz.*, azithromycin, cobicistat, HCQ, enoxaparin, and darunavir were administered. Seven patients out of eight have shown improvement in the Horowitz index and a continued reduction in C-reactive protein (an inflammatory parameter) and serum amyloid-A levels. Patients receiving this combined medication were discharged from the hospital within 14 days.[203] In one more study, sarilumab is administered to 53 severely infected patients who were hospitalized; 94% of the patients were also treated with HCQ and 70% were also treated with darunavir/ritonavir. In this study, 14/53 were treated in ICU while 39/53 were treated in medical wards. The condition of 90% of patients treated in medical wards was improved, while 39% remained alive and treated in ICU; the mortality rate is 5.7% in this clinical

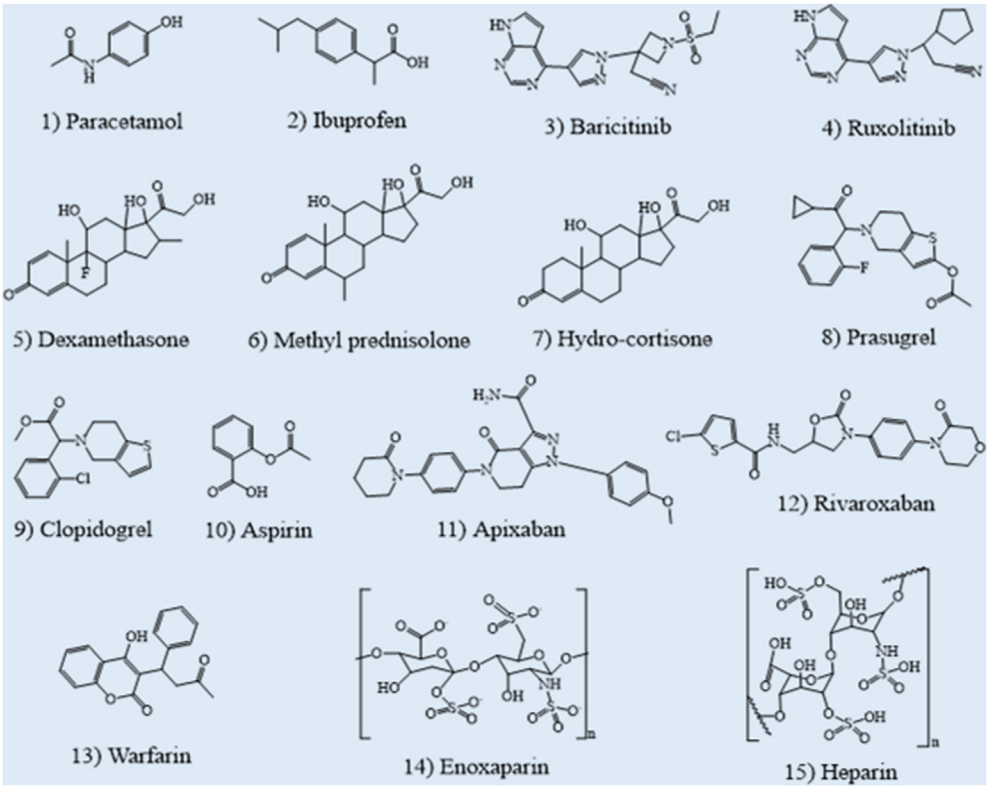

Figure 5 Chemical structures of repurposed anti-inflammatory, anti-platelet, and anti-coagulant molecules. Chemical structures of potential anti-inflammatory agents (serial number 1 to 7) such as corticosteroids (dexamethasone, methylprednisolone, and hydrocortisone), JAK inhibitor (baricitinib), and COX-2 inhibitors (paracetamol and ibuprofen). Serial number 8 to 15 in the figure depicts the chemical structures of potential anti-platelet agents (prasugrel, clopidogrel, and aspirin) and anti-coagulant agents (rivaroxaban, warfarin, enoxaparin, and heparin). All the structures were drawn using chem-draw software.

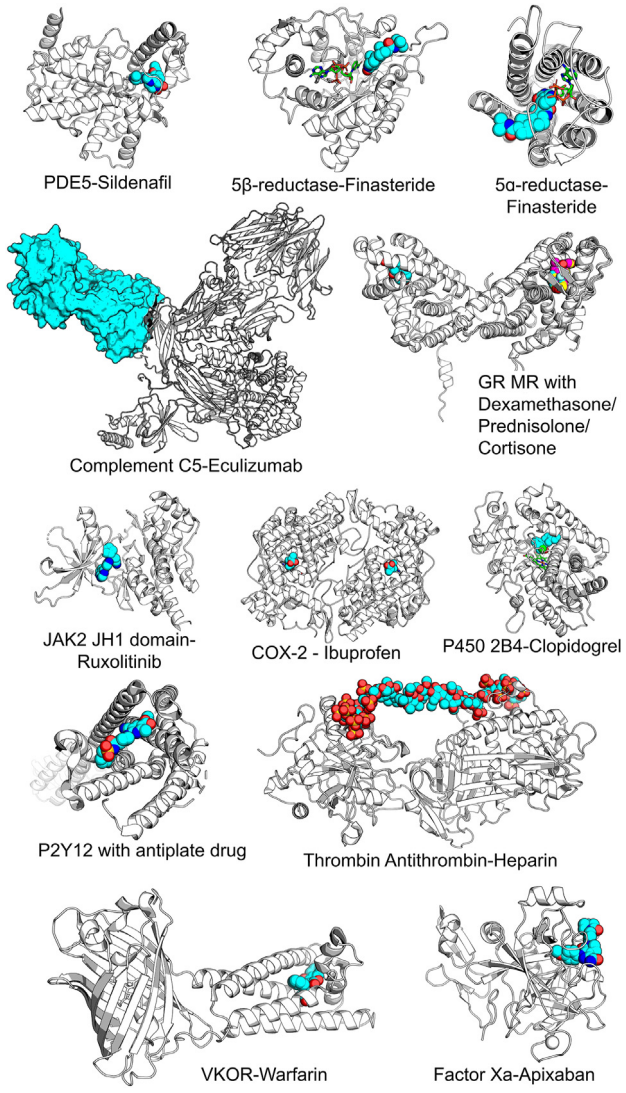

Figure 6 Structural details of host targets *vs.* drugs for alleviating the symptoms of SARS-CoV-2. PDE5 sildenafil complex (PDB: 2h42). 5β-Reductase Finasteride (PDB: 3g1r). 5α-reductase Finasteride (PDB: 7bw1). Complement C5 Eculizumab (PDB: 5i5k). Glucocorticoid mineralocorticoid receptors with bound drugs, dexamethasone, prednisolone, and cortisone (PDB: 2aax, 6nwk, 6w9k superimposed). JAK2 ruxolitinib complex (PDB: 6wtn). COX-2 ibuprofen complex (PDB: 4ph9). Antiplatelet drug clopidogrel bound to cytochrome P450 2B4 (PDB: 4h1n). P2Y12 bound to antiplatelet drug (PDB: 4ntj). Thrombin antithrombin heparin ternary complex (PDB: 1tb6). VKOR warfarin complex (PDB: 6wv3). Factor Xa apixaban complex (PDB: 2p16).

study.[204] Recently, a retrospective study was conducted to determine the efficacy of sarilumab in a group of 15 COVID-19 hospitalized patients. After sarilumab administration, 10/15 patients showed improvement in respiration while 5/15 patients died.[205] To date, all the clinical studies of sarilumab use were conducted on a limited number of patients. Thus, more research is needed on a large group of patients to determine its efficacy and to modify its use in emergencies.

Clinical studies showed the increase in IL-6 level in untreated COVID-19 patients and its decrease after treatment, suggesting its use in the treatment of SARS-CoV-2 infection helps reduce the cytokine storm. However, the relatively small sample size and a lesser number of relevant studies make these results less trustworthy for clinical administration.[205] Thus, much deeper studies and clinical trials are needed in near future to confirm patients' outcomes.

COX-2 inhibitors

Cyclooxygenase-2 (COX-2) inhibitors — known as non-steroidal anti-inflammatory drugs (NSAIDS). Paracetamol and ibuprofen are two COX-2 inhibitors used for symptomatic relief in COVID-19 complications. COX-2 inhibitors are mostly preferred in the early stage to treat symptoms *viz.*, fever and muscle pains, as per the EMA 2020 guidelines.[206] At the beginning of the COVID-19 outbreak, the role of COX-2 inhibitors is misjudged due to some contradictory results.[207] As a concern to treat the fever, the French Ministry of Health recommended paracetamol for patients instead of ibuprofen and oral cortisone.[208] After this announcement, some clinical reports were published related to its use in COVID-19 patients. Recently, a retrospective cohort study was completed in a group of 403 COVID-19 patients. In this study, 87/403 patients were treated with ibuprofen and the rest served as controls. No significant changes were found in mortality rate and requirement for respiratory support for ibuprofen use in comparison to paracetamol.[209] Furthermore, another multicentric observational clinical study was performed in a group of 1222 hospitalized COVID-19 patients. In this study, 54/1222 patients were continuously treated with NSAIDS prior to their hospitalization; besides their fever-lowering effect, there was no evidence related to an increase in mortality rate.[210] Based on EMA recommendations and clinical reports, paracetamol is used as a first-line drug to control fever in COVID-19 patients.

JAK inhibitors

Baricitinib and *Ruxolitinib* — two JAK inhibitors under evaluation for their reduction in hyper-inflammation in COVID-19 patients. On the other hand, monoclonal antibody eculizumab is clinically evaluated in combination with these JAK inhibitors in a few studies. JAK inhibitor baricitinib acts through two possible mechanisms *viz.*, reduction of the cytokine storm and inhibition of the intracellular assembly of SARS-CoV-2 in the host cells.[211] Recently, a clinical study was completed in a group of 12 mild to moderate COVID-19 patients with pneumonia; clinical improvement was found after two weeks of baricitinib use and none of the patients required ICU support in hospital.[212] In addition, another observational, multicentric, retrospective study of baricitinib and lopinavir/ritonavir (n = 113) combination was completed by the same research group in the moderate COVID-19 patients with pneumonia, which indicates its better performance in comparison with HCQ and lopinavir/ritonavir (n = 78) combination treatment. Patients treated with baricitinib and lopinavir/ritonavir combination showed a reduction in fatality rate and ICU admissions.[213] No such conclusion from this available data is drawn for the use of baricitinib in COVID-19 treatment. Furthermore, it could increase the

risk of common infections like herpes zoster. That is why one Italian researcher suggested the use of baricitinib should be done with absolute cautions.[214,215] On the other hand, ruxolitinib inhibits both JAK1 and JAK2.[216] Its safety and efficacy are currently under clinical trial (NCT04377620) for COVID-19.[217] Recently, two more clinical studies were documented with better efficacy of roxolitinib and eculizumab combination in hospitalized COVID-19 patients.[218,219] Eculizumab inhibits the terminal region of the complement cascade that is involved in inflammation. Recently, another study performed on three COVID-19 patients shows a marked reduction in neutrophil count and D-dimer level after the treatment with eculizumab.[219] Furthermore, another study shows an 82.9% survival rate in ICU patients treated with eculizumab, while a 62.2% survival rate was observed in non-eculizumab-treated patients. Eculizumab is also reported with an immediate reduction in blood urea nitrogen, lactate, and bilirubin levels; while the platelet counts and prothrombin levels were rapidly increased after eculizumab administration. Along with this, this study showed the holdback of hypoxia development after the administration of eculizumab.[218]

Kinase inhibitor baricitinib is preferred in COVID-19 patients with a dose of 2—4 mg/day. Its use is found to be risky in patients with neutrophil and lymphocyte counts less than 1×10^9 cells/L and 0.5×10^9 cells/L, respectively. Due to this, the chance of infection progression is increased in patients with lymphocytopenia. It also causes anemia in several treated patients. All these disadvantages and risk factors make its use confined to special medical conditions. However, no such potential effects of baricitinib are observed in patients elder than 75 years. A higher mortality rate is also observed in baricitinib-treated patients. Risk of infection reactivation is also observed in baricitinib-treated patient groups.[218,219]

Many anti-inflammatory drug molecules have been tested against COVID-19, but no such specific concluding remark is available to date. In addition, some reports have limitations in their observations *viz.*, small sample size and insufficient controls. Some reports do not mention the ultimate effect in terms of viral load and mortality rate. Thus, detailed, randomized, controlled, well-designed trials are needed to be performed to make any conclusive remark for its use.

Anti-platelet drugs

Aspirin, Clopidogrel, and *Prasugrel* — Aspirin[220] and $P2Y_{12}$ receptor antagonists (clopidogrel and prasugrel[221]) are clinically evaluated for their activity against COVID-19 (Fig. 5, 6). Generally, aspirin is used in myocardial infarction (MI), pre-eclampsia in pregnant women, and strokes for its irreversible inhibitory activity.[222,223] Instead of this, aspirin is documented for antiviral activity against both DNA and RNA viruses and in multiple human coronaviruses.[224] It acts by inhibiting thrombo-inflammation, resulting in the reduction of mortality rate and clinical complications.[224] Recently, an observational study showed its benefits (*viz.*, reduction in the mortality rate of the patients with acute lung injury and acute respiratory distress syndrome) in a small group of ICU-admitted patients,[225,226] while another similar study in a larger group of patients did not show any significant clinical improvement.[227] Furthermore, a double-blind, randomized, placebo-controlled clinical trial showed no such clinical improvement in acute respiratory distress syndrome (ARDS).[228] A retrospective cohort study was further conducted in hospitalized COVID-19 patients to investigate the effect of aspirin over the mortality rate, ICU admissions, and mechanical ventilation; a reduction in these aspects after treatment was found, but no such difference was observed in bleeding between treated and non-treated patients.[229] The University of Oxford is going to conduct the world's largest clinical trial in hospitalized COVID-19 patients, to determine the reduction in blood clotting after aspirin use. If it is found effective, then aspirin will be used as a safe and inexpensive medication to prevent blood clotting in COVID-19 patients.[230]

Generally, alveolar damage and endothelial dysfunction occur in most COVID-19 patients which contributes to hypoxic respiratory failure. This is associated with more severity and risk of death. Based on these life-threatening symptoms, L. Sacco University Hospital in Milano, Italy has registered (Trial no. NCT04368377[231]) and conducted a single center, case-controlled, phase-IIb clinical study of anti-platelets (aspirin and clopidogrel) in a group of severe COVID-19 patients. They observed no such significant adverse effect of anti-platelet drugs and found improvement in ventilation/perfusion ratio in severe patients. Furthermore, the $P2Y_{12}$ inhibitor prasugrel is still under clinical trial (Trial no. NCT04445623[232]) to evaluate its effectiveness in severe COVID-19 patients with pneumonia.

Anti-coagulants

Coagulopathy is a serious COVID-19 clinical complication, along with respiratory failure which may lead to death.[233] The pattern of coagulopathy is quite similar in patients with increased D-dimer and fibrinogen levels, mild thrombocytopenia, and mild progression of PT/aPTT. The exact mechanism of coagulopathy is not completely studied yet.[234,235] Generally, both coagulation and inflammation are linked to each other through various signaling pathways. Leukocyte adhesion molecules, intracellular tissue factor, and plasminogen activator inhibitor-1 (PAI-1) are stimulated by pro-inflammatory mediators.[236] Furthermore, inflammation can overexpress thrombin to activate the coagulation cascade in the lungs, resulting in fibrin deposition and progressive tissue damage. Moreover, SARS-CoV-2 can also directly damage the vascular endothelial cells and lead to coagulopathy.[237] A better understanding of coagulopathy in COVID-19 patients could help clinicians to diagnose and treat the patients.[238,239] In order to collect clinical evidence on the efficacy of anti-coagulants in COVID-19, an observational study was documented which shows the reduction in mortality rate and less requirement of mechanical ventilation of patients treated with anti-coagulants.[240]

Heparin (unfractionated or low molecular weight *Heparin*) — a major anticoagulant drug that reduces hypercoagulability in COVID-19 patients. Heparin could also act by neutralizing cytokines and chemokines, blocking

heparinase activity, neutralizing extracellular cytotoxic histones, hampering leukocyte trafficking, and inhibiting viral entry to host cells. Thus, heparin can block both inflammation and coagulation.[241,242] Furthermore, heparin is documented for anti-inflammatory activity in COVID-19 patients by increasing lymphocyte count and reducing IL-6 level.[242] One more observational study of its effectiveness was documented further and reported a reduction in the mortality rate of hospitalized patients treated with heparin.[243]

Enoxaparin (low molecular weight heparin: LMWH) — recommended by WHO in treating COVID-19 hospitalized patients having chances to develop venous thromboembolism.[244] The debate still exists on the use of optimum anticoagulant doses. WHO has recommended the prophylactic dose of LMWH in hospitalized patients rather than non-hospitalized patients.[236,244,245] Based on several protocols and local experiences, the American Society of Hematology has decided on its intermediate dose (administered daily, twice a day).[246] Another guideline has recommended that the doses may vary according to the body weight in acute or critically ill patients. This guideline has mentioned the priority to use unfractionated heparins over LMWH in COVID-19 patients because some patients have bleeding problems with LMWH.[247] To observe the bleeding problem due to LMWH, a recent retrospective cohort study was conducted in a dose-dependent manner and concluded that a therapeutic dose of LMWH does not cause the bleeding issue in COVID-19 patients.[248] Based on this evidence, these anticoagulants (Figs. 5 and 6) are used to prevent coagulopathy in COVID-19 patients.[236] Several ongoing clinical trials are started to study the efficacy and safety for use of anticoagulants in COVID-19 patients.

Natural product-based molecules

From ancient times, plants are considered a major source of new chemical entities (NCEs) to fight against several diseases. In past pandemics like MERS, SARS, influenza, and dengue, several herbal medicinal plants have been found effective. Health departments of several countries are approving and exploring the benefits of antiviral plant products alone or in combination with standard antiviral therapeutic agents to win against COVID-19.[249] It is also documented that plants' secondary metabolites are effective in the prevention of viral replication.[250–252]

A research group screened a medicinal plant database containing 32,297 antiviral medicinal phytochemicals and traditional Chinese therapeutic agents and selected the top nine molecules with inhibitory potential on $3CL^{pro}$ activity that works against replication of SARS-CoV-2. The top five compounds *viz.*, 5,7,3′,4′-tetrahydroxy-2-(3, 3-dimethylallyl) isoflavone, myricitrin, methyl-rosmarinate, calceolarioside-B, and licoleafol showed very good docking score and binding affinity compared to the positive controls (nelfinavir and prulifloxacin). Authors have concluded that these phytochemicals could serve as potential lead molecules to fight against COVID-19.[253] Another group has also screened medicinal plants and natural products through computational study, and a retrospective cohort study was conducted on four COVID-19 patients at Shanghai Public Health Clinical Center to evaluate the efficacy of traditional Chinese medicine (*Shufeng Jiedu* capsule) with arbidol and lopinavir/ritonavir combination. *Shufeng Jiedu* capsule is also recommended to treat pneumonia in the early stage of COVID-19. Although these results are encouraging, further validations are needed to be done.[254,255] In the following section, we are interested to discuss on a few important medicinal plant products that exhibit antiviral activity and are also used in the Ayurvedic system of medicines, the Chinese traditional system of medicine, and Unani, and as a prophetic medicine.

Thymoquinone — an active constituent present in the seeds of *Nigella sativa* plant that has a number of pharmacological properties and is used in multiple diseases. Thymoquinone is also documented for its antiviral activity. One research group compared thymoquinone activity with chloroquine/hydroxychloroquine (CQ/HCQ) and showed that the antiviral mechanism of action of both drugs is more or less the same. Also, thymoquinone has a wider antiviral spectrum and no side effects while CQ/HCQ has side effects and less antiviral spectrum. Additionally, they also mentioned that thymoquinone (a hydrophobic drug) has the capability of killing SARS-CoV-2 virus by binding to its lipophilic pocket.[256] Another study has revealed that nigellimine and thymoquinone may be capable of inhibiting SARS-CoV-2 entry through ACE2 receptors. They also mentioned that zinc supplementation may enhance the antiviral activity of several active therapeutic molecules.[256] Recently, it has been suggested that the use of *Nigella sativa* as an adjuvant in combination with HCQ reduces its toxicity and enhances antiviral activity.[257] An interesting study of *Nigella sativa in* comparison with CQ based on docking, simulation, and MM-PSBA found that dithymoquinone (an active constituent of *Nigella sativa*) was much more effective than CQ.[258] Currently, a randomized, open-label, controlled, phase-III clinical trial for the effectiveness of *Nigella sativa* in combination with honey is under progress in Pakistan.[259] A phase-II (NCT04401202) clinical trial of *Nigella sativa* seed oil for determining its efficacy in upper respiratory tract infection is under progress.[260]

From the ancient time, several other plants *viz.*, cinchona, wintercherry, eldercherry, liquorice, turmeric, ginger, pomegranate, and green chiretta are widely utilized in the Indian system of medicines against upper respiratory tract infections. These medicinal plants with antiviral activity against several infections may also be effective against SARS-CoV-2 infection. *Cinchona succirubra* belongs to the Rubiaceae family and contains quinine as a chief active constituent and has antiviral activity against herpes simplex virus-1 (HSV-1) and influenza A virus (IAV).[261] *Sambucus nigra* belongs to the Caprifoliaceae family contains ursolic acid as a chief active constituent and has antiviral activity against herpes virus.[262] *Withania somnifera* belongs to the Solanaceae family and contains withanolides and withaferins as chief active constituents and has antiviral activity against herpes simplex virus and H1N1 influenza virus respectively.[263] *Prunella vulgaris* belongs to the Lamiaceae family and contains betulinic acid and hyperoside responsible for antiviral activity against HIV-1 and Ebola virus[264] while delphinidin present in plants has antiviral activity against herpes simplex virus-1 and -2.[265]

Glycyrrhiza glabra belongs to the Fabaceae family and contains glycyrrhizin that acts against hepatitis C-virus and glycyrrhetic acid and liquiritin that act against influenza virus and iso-liquiritin that acts against HSV-1.[266] *Caesalpinia pulcherrima* belongs to the Leguminosae family and contains lupeol with antiviral activity against herpes virus and adenoviruses.[267] *Curcuma longa* belongs to the Zingiberaceae family and contains gingerol which is effective against avian influenza (H9N2) virus.[268] *Punica granatum* belongs to the Lythraceae family and contains punicalagin and ellagitannin having antiviral effectiveness against SARS-CoV viruses.[269] *Andrographis paniculate* belongs to the Acanthaceae family and contains andrographolide with antiviral properties against HSV, hepatitis B and C viruses, HPV, HIV, and chikungunya virus.[270,271] These herbal medicinal plants may also be effective against SARS-CoV2 infection, hence important to be repurposed for COVID-19 treatment. Here we have demonstrated the clinical advancements along with the mechanism of action of repurposed important plant ingredients. We found that some limitations are still in the conduction of clinical trials with limited sample size and contradictory results in addition to the data generated in specific regions across the globe. Hence, clinicians and researchers should have to innovate and work more to sort it out.

Limitations, challenges, feasibility, and possible solutions associated with repurposed drugs

Instead of several efforts and research in the area of drug repurposing against COVID-19, multiple issues related to drug dosage, safety, and delivery still exist. Several clinical trials have suggested the use of repurposed drugs against this infection in a specific therapeutic dose margin. It has been rarely documented to discover newer drug—target interactions within this therapeutic window. If a higher dose of a drug is required to achieve a certain amount of efficacy, the concept of administration route may be considered to further promote the progress of these drugs. If the dose utilized to exert a specific range of efficacy is higher than the therapeutic window, the determination of the safety of those drugs needs to be done. Thus, the achievement of therapeutic benefits by using the dose within the therapeutic margin is not feasible in every case.[272]

Often, a higher dose is required to achieve the antiviral activity in multiple documented clinical studies. Most clinical studies were conducted in a smaller sample size which made it difficult to conclude trustworthy efficacy. Often, a few clinical studies are required for drug repurposing but therapeutic efficacy is a necessity. To achieve higher efficacy, the route of administration is also an important measure to be considered. For that reason, the mode of administration is changed from the specified one. However, the stability of these drugs is also an important issue observed in clinical reports, which can be improved by using specific carrier systems.[273—277]

Physicochemical properties (*viz.*, solubility, permeability, lipophilicity, *etc.*) of these drugs could make it difficult to achieve favorable clinical outcomes. The efficacy of most drugs is not up to the mark to achieve a better outcome. Thus, the release modification of these drugs is needed to improve their therapeutic efficacy. Several other factors related to the pharmacokinetics and bio-transformation of these drugs also need to be taken care of. To date, no guidelines are approved by regulatory bodies regarding drug repurposing. Hence, it is not easy for newer start-ups to give suitable information to regulatory agencies, which causes a major difficulty in drug repurposing.[274,278]

Success in drug repurposing is achieved through the administration of drugs via suitable routes and delivery system. The selection of right dose, right delivery system, and the right mode of administration needs to be taken care of during their formulation. To achieve this, the integration of pharmaceutical sciences and toxicology is needed to make safer localized and targeted drug delivery.[279] Especially, in the case of respiratory viruses, the focal delivery of drugs through the appropriate device can improve the efficacy of these drugs and limits their exposure to other tissues. Pulmonary delivery of these drugs can be achieved through the drug aerosols which can enhance drug concentration in the lungs, lower side effects, and may improve efficacy.[280] Through this drug delivery approach, the first-pass metabolism of these drugs can be lowered or avoided.[273] Drugs hydroxy-chloroquine and niclosamide are under development in the form of aerosols to improve absorption and focal drug delivery and to reduce adverse effects. These are also tested to have their better efficacy and improvement in severe SARS-CoV-2 infected patients.[281]

Generally, these drugs are well established and clinically proven with good efficacy towards their primary target but lesser efficacy is observed against the secondary target. A similar thing happens in the case of repurposed drugs against SARS-CoV-2 infection. To enhance the efficacy of these drugs, re-formulation or modification of these drug molecules are needed; as a result, the efficacy of these drug molecules can be improved.[282]

Modifications in formulation, delivery route, and chemical and physicochemical properties are difficult, challenging, and time-consuming in front of this COVID-19 pandemic, but scientists, clinicians, and pharmaceutical companies are still working in an integrative manner to achieve these goals for the welfare of humanity.

Target-based drug discovery: a future approach

To date, no such drug is available that acts specifically against SARS-CoV-2 infection and COVID-19 treatment. Researchers and pharmaceutical industries are trying to develop new chemical entities (NCEs) and repurpose existing potential therapeutics, but target-based drug development should be an ideal strategy.[276,283] Here in this section, we want to draw kind attention of scientists and pharmaceutical companies toward the probable future approach for the development of target-based drugs (Fig. 7).

Spike glycoproteins

Viral particles like SARS-CoV-2 contain spike glycoproteins on their surface that play a crucial role in the recognition

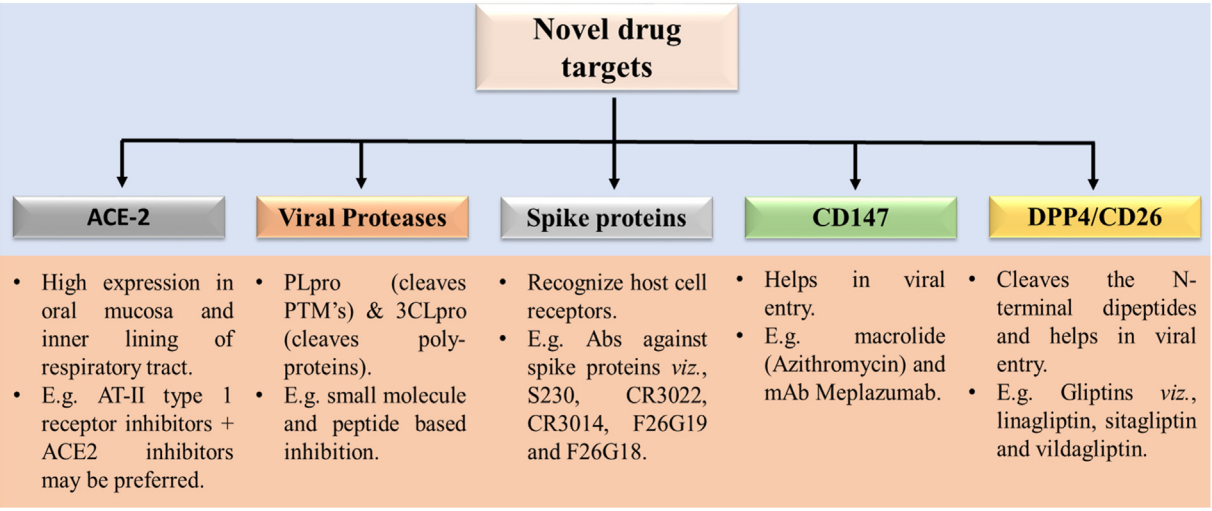

Figure 7 Future novel drug development strategies against SARS-CoV-2. The figure depicts the predictive novel drug development strategies (by targeting ACE-2, viral protease, spike proteins, CD147, and DPP4/CD26) that may be preferred in near future.

and attachment to host cell receptors (*viz.*, ACE2, CD147, and TMPRSS2) for entry and maintaining viral life cycle. Spike proteins should be important targets for the design of drugs and antibodies for preventing the entry of SARS-CoV-2 into the host cells, thus they may be worthy and lifesaving drug targets for industries to design new drugs.[284] Recently, researchers successfully designed some therapeutic antibodies against the viral spike proteins of SARS-CoV-2 *viz.*, S230, CR3022, CR3014, F26G19, and F26G18.[285]

Viral proteases

Papain-like protease (PLpro) and 3C-like protease (3CLpro) are two crucial proteases that may be important drug targets in SARS-CoV-2 infections.[286] 3CLpro helps in the cleavage of poly-proteins at 11 sites with the Leu—Gln recognition sequence, while PLpro helps in the cleavage of post-translational modifications of host proteins.[287] Both proteases play a crucial role in polypeptide processing and viral replication. Thus, targeting these proteases could be an effective and novel strategy to treat COVID-19. Several therapeutic agents *viz.*, pyrazolone derivatives, α-ketoamide inhibitors, cyclohexyl methyl, and 1,3,4-oxadiazole disulfide are being evaluated *in vitro* for their inhibitory activities against SARS-CoV-2 infections. Several pieces of the literature suggest that targeting PLpro and 3CLpro could be a life-saving strategy against SARS-CoV-2 infection.[287,288]

Cell surface protein DPP4

Glycoprotein dipeptidyl-peptidase-4 (DPP4) is not only expressed in immune cells but also expressed and localized on the surface of endothelial cells, mononuclear lymphoid cells, type I and II lung parenchyma cells and in macrophages. It is also expressed in endothelial and epithelial cells of the small intestine, kidneys, spleen, heart, vascularized smooth muscle cells, pancreas, hepatocytes, and monocytes. It is mostly present in blood plasma and various body fluids. It acts as a peptidase to cleave the N-terminal dipeptides of various substrates (*viz.*, growth factors, neuropeptides, cytokines, vasoactive peptides, and incretin hormones). In most cases, cleaved substrates are found to lose their biological activity. Furthermore, patients with chronic lung diseases were reported with high expression of DPP4 in alveolar epithelium, type I and II alveolar cells, and alveolar macrophages. These results suggest that high expression of DPP4 in immune and vascular endothelial cells may contribute to SARS/MERS-related diseases.[289,290]

Currently, it is well established that SARS-CoV-2 uses the ACE2 receptors to enter the human body.[291] DPP4 is highly expressed in the respiratory tract and recent studies have demonstrated that it participates in SARS-CoV-2 entry like ACE2 receptor.[292] Recently, one more interesting report has demonstrated the correlation between ACE2 and DPP4, indicating that both the cell surface proteins are responsible for SARS-CoV-2 entry.[293] The correlation between DPP4 and MERS-CoV infection is well established, where DPP4 expression is documented to produce lung inflammation because it acts as a pro-inflammatory molecule.[294,295] Currently, a similar type of correlation between DPP4 and SARS-CoV-2 is not well established yet due to a lack of pathological information but DPP4 caused lung inflammation in SARS-CoV-2 infection.[292,296] Both SARS and MERS caused fatal pneumonia and acute respiratory distress syndrome (ARDS) and are responsible for the initiation of cytokine storms and a similar type of immunopathology.[297—300] DPP4/CD26 inhibition could prevent pulmonary inflammation. Thus, DPP4 acts as a co-modulator of the life-threatening impact of SARS-CoV-2. Inhibition of DPP4 may contribute to the prevention of SARS-CoV-2 entry and COVID-19 complications. The development of novel and effective DPP4 inhibitors should be a strategic plan for COVID-19 treatment.[295,301—306] A number of commercial DPP4/CD26 inhibitors (gliptins) are already available in the market *viz.*, linagliptin, sitagliptin, and vildagliptin.[275,307] To prevent SARS-CoV-2 infection, DPP4/CD26 inhibitors gliptins work through four possible mechanisms: (i) reduction in cytokine storm,[295,303,308,309] (ii) reduction in the activity and functions of macrophages,[310]

(iii) induction of anti-inflammatory signaling molecules such as GLP-1 (especially in elder patients),[311,312] and (iv) induction of anti-inflammatory effects.[313,314] These drugs may be a lifesaving weapon for fighting against COVID-19. Thus, DPP4/CD26 may be an interesting, potential, and worthy drug target for pharmaceutical industries.

Angiotensin converting enzyme-2 (ACE2)

ACE2 receptors are highly expressed in oral mucosa and the inner lining of the respiratory tract; this is why the ACE2 receptor is the primary target for drug development against SARS-CoV-2. ACE2 enzyme is responsible for the conversion of angiotensin-I to angiotensin-II. Researchers have developed a human recombinant soluble ACE2 receptor for the management of pulmonary hypertension and for an acute pulmonary injury which is under clinical trial. The use of this recombinant soluble ACE2 receptor may be a potential strategy to prevent SARS-CoV-2 spread in early stages.[315] Individual use of ACE2 inhibitors will not be able to prevent SARS-CoV2 infection. It is also documented that chronic treatment with selective angiotensin II type 1 receptor inhibitors lisinopril, losartan, and olmesartan promotes gene expression of ACE2 receptors in the kidney and heart, leading to severe respiratory syndrome after SARS-CoV-2 infection.[316] The increased ACE2 level promotes more conversion of angiotensin I to angiotensin-II, which may lead to severe lung impairment.[317] Thus, the combination of angiotensin receptor blockers with ACE2 inhibitors may be a potential and effective strategy for COVID-19 treatment by reducing vasoconstriction, cardiac stress, and pro-fibrotic effects of angiotensin-II in lungs.[318] Thus, researchers and pharmaceutical industries must draw their attention to this strategy for drug discovery for COVID-19 treatment.

Membrane fusion protein CD147

Like ACE2, a fusion protein CD147 also helps in SARS-CoV-2 entry and plays a crucial role in pathogenesis.[97] As discussed earlier, meplazumab is a monoclonal antibody that acts as an inhibitor of fusion protein CD147. Currently, meplazumab is under a clinical trial, registered with clinical trial numbers NCT04275245[99] and NCT04586153.[100] Ongoing clinical trial studies are mostly focused to determine its safety and efficacy on COVID-19 patients. Thus, the discovery of additional new molecules and the use of existing therapeutic agents against CD147 fusion protein may be a potential strategy to treat present and future COVID-19 patients.

The existing macrolide antibiotic azithromycin is being evaluated as a potential inhibitor of CD147 fusion protein. Azithromycin prevents the binding of spike proteins to CD147 receptors, leading to the inhibition of the entry of virus particles. Prolonged use of azithromycin is also documented to reduce the expression of metalloproteinases downstream to CD147. Mild side effects were also noticed during its use such as headache, dizziness, abdominal pain, and mild gastric upset.[97] Furthermore, as reported, mild respiratory tract fibrosis in early COVID-19 patients leads to serious whole lung fibrosis in the later phase of treatment and may lead to occasional death due to respiratory failure. Additionally, CD147 monoclonal antibody inhibits the TGF-β1 expression and leads to the inhibition of the proliferation and differentiation of human lung fibroblasts. Moreover, the transplantation of allogeneic mesenchymal stem cells of the healthy donors was evaluated to induce immunosuppression and tissue regeneration in COVID-19 patients with lung injury.[319–321] Thus, targeting CD147 may be a new hope for clinicians to save the world from this devastating disease.

Conclusions

The COVID-19 pandemic is a global threat as there is no specific and effective treatment available. Currently, clinicians and researchers are mostly preferring the repurposing of drugs as a gold standard strategy to provide symptomatic relief and prevent infection and death from this highly infectious disease. Various classes of drug molecules such as antiviral agents, anti-inflammatory agents, corticosteroids, antibiotics, anti-coagulants, anti-platelets, and various traditional herbal plants are repurposed for treatment alone or in a combinatorial approach for a better outcome. We have highlighted the clinical trial status of each of these repurposed drugs available to date, and their pharmacological mechanisms. Some of these drug molecules have better bioavailability and effectiveness, whereas many of them are not good at all. As discussed above, most of the drugs are still in the various stages of clinical trials and some are approved by respective regulatory authorities for their clinical use. Some drugs have their limitations in the conduction of clinical trials such as limited sample size, non-availability of geographical effectiveness, non-availability of standard doses, and proper controls used in their studies. Thus, researchers and clinicians will have to put more effort into their clinical trial limitations and much more attention is required in this area. This report has demonstrated the past (literature), present (clinical status) and future (probable drug design and development) strategies for COVID-19 treatment. Investors and pharmaceutical industries need to come together for innovation, and they must focus on future drug discovery strategies for the development of more specific and effective new treatment options.

Author contributions

SK and MKG conceived the idea and review structure, wrote the manuscript, and prepared the figures and tables; UP prepared Figure 3 and 6; SK, MB, and MKG revised and edited the manuscript. All authors read, agreed, and approved the final draft of the manuscript.

Conflict of interests

The authors declare that there are no competing interests.

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