

Review

Clinical Efficacy and Safety of Antiviral Drugs in the Extended Use against COVID-19: What We Know So Far

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Abstract: Human beings around the globe have been suffering from a devastating novel pandemic and public health emergency, coronavirus disease 2019 (COVID-19), for more than one and a half years due to the deadly and highly pathogenic severe acute respiratory coronavirus 2 (SARS-CoV-2) infection worldwide. Notably, no effective treatment strategy has been approved for the complete recovery of COVID-19 patients, though several vaccines have been rolled out around the world upon emergency use authorization. After the emergence of the COVID-19 outbreak globally, plenty of clinical investigations commenced to screen the safety and efficacy of several previously approved drugs to be repurposed against the SARS-CoV-2 pathogen. This concise review aims at exploring the current status of the clinical efficacy and safety profile of several antiviral medications for the treatment of patients with COVID-19 and other respiratory complications caused by SARS-CoV-2 infection. The paper covers all kinds of human studies (January 2020 to June 2021) except case reports/series to highlight the clear conclusion based on the current clinical evidence. Among the promising repositioned antivirals, remdesivir has been recommended in critical conditions to mitigate the fatality rate and improve clinical conditions. In addition, boosting the immune system is believed to be beneficial in treating COVID-19 patients, so interferon type I might exert immunomodulation through its antiviral effects by stimulating interferon-stimulated gene (ISG). However, more extensive clinical studies covering all ethnic groups globally are warranted based on current data to better understand the clinical efficacy of the currently proposed repurposed drugs against COVID-19.

Keywords: coronavirus disease 2019 (COVID-19); repurposing strategy; repurposed drugs; remdesivir; interferon type I; clinical trials

1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has created a lot of burden on the global medical system, public health, and economic and social life of human beings [1,2]. The causative pathogen identified for COVID-19 is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged from viruses of unknown sources [3,4].

SARS-CoV-2 is a type of β -coronavirus (β -CoV) that belongs to the coronavirus group. The human coronavirus group causes several outbreaks, including the severe acute respiratory syndrome (SARS-CoV) epidemic from 2002 to 2004 and the Middle East respiratory syndrome (MERS-CoV) outbreak in the Middle East, Africa, and South Asia, and many more countries during 2012 [5,6]. Wuhan, China, was the first city for the occurrence of COVID-19, and after that, it spread all over the world, infecting around 218 million people together with over 4.5 million total deaths, according to the COVID-19 global case dashboard of the World Health Organization (WHO), by 29 August 2021 [7]. Based on the data from January 2020, the WHO declared COVID-19 a Public Health Emergency of International Concern (PHEIC), which was followed by a pandemic on 11 March 2020 [8].

In the meantime, many vaccines have received emergency use authorization, and by 30 August 2021, 5.24 billion doses had been administered globally. Around 40% of the world population has received at least one dose of the COVID-19 vaccine. It is notable that approximately 39 million people are taking the COVID-19 vaccine per day. However, only 1.6% of people from low-income countries have received at least one dose of the vaccine to be inoculated [9]. In addition, the production and equitable distribution of a large number of vaccine doses is challenging for world leaders to achieve within a short time. Another concern is that political and financial matters might be a significant barrier to administering the vaccines to the entire world population for all ethnic and socioeconomic groups. The development and production of the vaccines within a very narrow time frame might have implied insufficient evidence for the safety and efficacy of the vaccines in the long term [10]. Therefore, the world community must develop new effective and safe antiviral drugs or therapeutics to fight against COVID-19.

To date, no effective and approved antiviral treatment is available to fight against COVID-19. However, some recommendations are being practiced concurrently to manage individual patients' needs, such as antipyretic drugs for fever, oxygen therapy for respiratory distresses, antimicrobial therapy with mechanical ventilation applied in some severe cases depending on the clinical condition of the patient, and so on [11,12]. Meanwhile, the drug repurposing strategy is being continuously used in COVID-19 treatment. Drug repurposing or drug repositioning is tactically a rapid process to identify new pharmacological indications rather than the original purpose of investigational, existing, already marketed or FDA-approved drugs for the treatment of diseases. This advantageous method provides a great benefit in circumventing some *de novo* drug design and development stages. Thus, the technique decreases scheduled periods of drug development, reduces failure risk, and protects funds from being wasted [13]. In addition, it is crucial for a drug to be effective, proportionally related to clinical efficacy, or to produce desired pharmacological activities for a specified indication in humans. A potential drug must be passed through efficacy trials to fulfill the principal requirements of clinical efficacy, including several human trial phases [14]. In other words, efficacy trials determine the possibility of an intervention to produce expected results under ideal circumstances or the degree of beneficial effects under real-world clinical settings [15,16].

More importantly, SARS-CoV-2 is the seventh member of the genus β -coronavirus and the *Coronaviridae* family [17]. Genome sequencing of SARS-CoV-2 demonstrated that the virus is almost 79% and 50% identical with the previous two SARS-CoV and MERS coronaviruses, respectively [18]. So, it might be very convenient and rational to repurpose the currently available antiviral drugs used against the two previous viral pandemics (SARS and MERS CoV) or have evidence of previous experience. Furthermore, it has been perceived that drug repurposing has already become a "universal strategy" to face the challenges of the COVID-19 pandemic because of several advantages it offers. These include fewer clinical trial steps, the availability of the formulation and distribution of the existing pharmaceutical supply, the possibility of more effective treatment of known combination therapy, the discovery of novel mechanisms of actions of old drugs or new classes of medicines, [19] and the elimination of "activation barriers" in the early stages of research, thus ensuring the rapid advancement of any project to disease-oriented research [20].

Several FDA-approved available antiviral drugs, alone or in combination, have been screened clinically for their extended use since the early phase of the current pandemic to find a safe and effective treatment option against COVID-19 [21,22], and many clinical trials of these antiviral drugs are still ongoing. However, an in-depth understanding is required from current clinical literature reports to execute integrated approaches between computational and experimental methods to guarantee high success rates of repositioned drugs. Moreover, multiple challenges associated with repurposed drugs have been identified, including dose adjustments, route of administration, acute/chronic toxicity, appropriate delivery systems, etc. [23,24]. Although many preliminary studies exhibited promising results, several extensive clinical investigations reported contradictory findings with significant adverse effects of these elongated applications of antiviral drugs. However, numerous clinical trials conducted with larger samples/patients have recently disclosed many mixed results, which needs careful study. Therefore, it is essential to review comprehensively the uses of repurposed drugs focusing on the therapeutic strategies, advantages, adverse drug reactions, and respective delivery approaches for instigating an instrumental battle against COVID-19. Likewise, it is also necessary to know the clear disease pathology and critical strategies to identify new drugs capable of protecting against highly contagious viral infections, including the SARS-CoV-2 infection [25]. This article summarizes the current understanding of clinical efficacy and the adverse drug reaction of various antiviral drugs used for SARS-CoV-2-infected patients across the world. Here, we also illustrated Figure 1 to represent the chemical structures of the seven repurposed antiviral drugs for use against COVID-19.

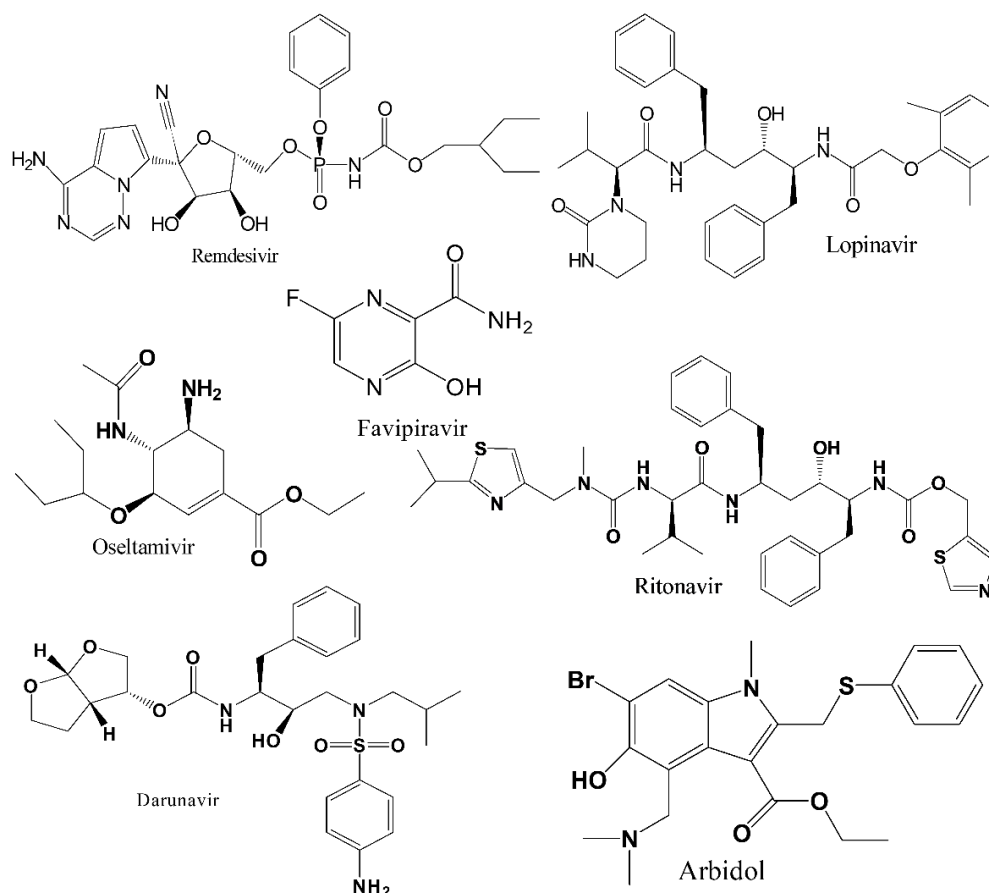


Figure 1. Chemical structures of the selected most promising antiviral drugs against COVID-19.

2. Methods

Search and Data Collection

The scientific articles published from January 2020 to June 2021 on several repurposed antiviral drugs that had potentiality against COVID-19 were downloaded from various databases such as Google Scholar, Semantic Scholar, PubMed, Scopus, Europe PMC, ScienceDirect Journals, SpringerLink, Wiley, Taylor & Francis, and so on, with several preprint servers. We utilized several suitable keywords and used those words individually or in combination to find the data regarding the target topic. The keywords included “COVID-19”, “coronavirus diseases 2019”, “SARS-CoV-2”, “clinical trials”, “observational study”, “cohort study”, “safety and efficacy”, “remdesivir”, “favipiravir”, “lopinavir/ritonavir”, “interferons”, “arbidol”, “umifenovir”, “oseltamivir”, “darunavir”, and so on. We included the human studies designed as randomized or non-randomized, open-label, controlled clinical trials, and observational or cohort studies to find a clear understanding of the safety and efficacy of repurposed antiviral drugs against mild, moderate, and severe cases of COVID-19. However, we excluded case reports or case series in this review paper. In addition, the current review rejected the data containing a limited number of subjects, weak statistical analysis, or vague conclusions.

3. Promising Antiviral Drugs against SARS-CoV-2: Results from Human Studies

3.1. *Remdesivir (RDV)*

Remdesivir (RDV, GS-5734), a nucleoside monophosphate analog, has emerged as one of the most promising clinically investigated drugs to treat SARS-CoV-2 infection from the beginning phase of the COVID-19 outbreak. RDV was preliminarily developed for treating acute Ebola virus disease [26]. Mechanistically, RDV acts as a broad-spectrum antiviral drug by inhibiting RNA-dependent RNA polymerase (RdRp) enzyme from restricting viral replication, and it has already shown its efficacy against SARS-CoV-1 and MERS-CoV through the improvement of lung infection [27,28].

Grein et al. [29] conducted a cohort study on 61 patients hospitalized with severe COVID-19 who were administered RDV as a compassionate therapy for 10 days (200 mg on the first day and 100 mg for the next nine days) and observed clinical improvement in 68% of patients ($n = 36$ out of 53). Antinori et al. [30] conducted another open-label, prospective study in Italy on 35 patients (ICU = 18 and non-ICU = 17) and observed a more beneficial effect on non-ICU patients after 10 days of therapy of RDV. Although the study recognized some mentionable adverse effects like acute kidney injury and hypertransaminasemia for 22.8% and 42.8% of patients, respectively, the study findings recommended a larger randomized controlled clinical trial to evaluate the safety and efficacy of RDV against COVID-19. Pasquini et al. [31] assessed the efficacy of RDV on 51 ICU-admitted patients of an average age of 67 years (IQR = 59.0–75.5), of which 25 were treated with the drug. The study reported that the RDV group showed a significantly lower fatality rate (56% vs. 92%, $p = 0.001$) and was associated with better survival (OR 3.506; 95% confidence interval (CI) = 1.768–6.954; $p < 0.001$). In another prospective observational study conducted on 48 COVID-19 patients with dialysis-dependent end-stage renal disease, Aiswarya et al. [32] concluded that early treatment with RDV (within 48 h) appeared to shorten recovery and discharge time with safety and good tolerability. In a comparative analysis of 1130 patients (RDV = 312 and non-RDV = 818), Olender et al. [33] reported that the drug exhibited a 15.4% greater recovery rate than in the non-RDV cohort group and reduced mortality by 4.9% in severe COVID-19 patients.

A randomized, placebo-controlled, double-blind clinical trial ($n = 1062$; RDV = 541 and placebo = 521) conducted by Beigel et al. [28] showed that those who took RDV exhibited lessened recovery time (10 days) than those with placebo (15 days), as well as a reduced mortality rate (RDV vs. placebo = 7.1% vs. 11.9%, respectively). Goldman et al. [34] conducted a phase 3, open-level control trial that displayed the potent antiviral activity of RDV against SARS-CoV-2, with some adverse effects such as nausea (9%), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%). A retrospective comparative study was carried out by Garibaldi et al. [35], which presented the result of a shorter improvement time in the test group than the control group. A large observational study evaluated no statistical difference in efficacy between the RDV and control group [36]. An open-level, randomized clinical trial with RDV initiated by Wang et al. [37] reported no significant clinical benefits and suggested more extensive studies to confirm numerical reduction time for clinical improvement patients in the earlier stage. In another comparative study [38], no statistically significant difference was reported between clinical status and standard care. Another placebo-controlled, double-blinded, randomized trial conducted by Kalil et al. [39] demonstrated the potential activity of the antiviral drugs against COVID-19. Falcao et al. [40] conducted an observational cohort study in Lisbon that compared remdesivir treatment to hydroxychloroquine treatment and their adverse effects. Hydroxychloroquine generated more adverse effects (47.5%) than RDV. In a real-life setting, the RDV regimen reduced hospitalization in both intubated (1.4 days less) and non-intubated (3.4 days less) patients, although it was not statistically significant [41]. A study compared the efficacy of remdesivir, convalescent plasma, and a combination of both, which eventually revealed a higher survival rate in patients receiving RDV only [42]. In addition, several more randomized controlled clinical trials are undergoing to ensure the safety and efficacy of RDV against COVID-19. All the above-mentioned study findings and details of randomized characterizations of RDV and other antiviral drugs are tabulated in Table 1.

Table 1. Summary of the latest clinical trials and observational studies to investigate the safety and efficacy several repurposed antiviral drugs against COVID-19.

Drug	Reference	Study Type	Country	<i>n</i>	ROA	Results	ADR	Interpretation
RDV	Beigel et al. [28]	RCT (NCT04280705)	USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore	1059 patients (T = 541 and C = 521)	IV	RDV showed shortened recovery time (from 15 to 11 days) and reduced mortality rate by 4.8%	Serious ADR: T vs. C = 24.6% vs. 31.6%	Warrants RCT
RDV	Grein et al. [29]	Cohort	USA, Europe, Canada, and Japan	61	IV	68% patients (<i>n</i> = 36 out of 53) showed clinical improvement	Multiple organ dysfunction syndrome, septic shock, acute kidney injury, and hypotension	Warrants RCT
RDV	Antinori et al. [30]	Open label (Observational)	Italy	35 patients (ICU = 18 and Non-ICU = 17)	IV	Observed more beneficial effect for non-ICU patients after 10 days of therapy	Hyper-transaminasemia and acute kidney injury	Warrants RCT
RDV	Pasquini et al. [31]	Retrospective	Italy	51 patients (T = 25, C = 26)	IV	Significantly reduced fatality rate (56% vs. 92%; <i>p</i> < 0.001) and improved survival rate (OR = 3.506, 95% CI = 1.768 to 6.954; <i>p</i> < 0.001)	NA	Significant survival might be associated with RDV use
RDV	Aiswarya et al. [32]	Cohort	India	48	IV	Early treatment of RDV (within 48 hrs) reduced recovery and discharge time with safety and good tolerability.	Acute kidney injury and hypotension	Warrants RCT
RDV	Olender et al. [33]	Open level (NCT04292899)	USA, Italy, Spain, Germany, Hong Kong, Singapore, S. Korea, and Taiwan	1130 patients (T = 312 and C = 818)	IV	RDV exerted 15.4% more recovery (adjusted odds ratio (aOR) = 2.03; 95% CI = 1.34–3.08, <i>p</i> = 0.001) and reduced mortality of 4.9% (aOR = 0.38; 95% CI = 0.22–0.68, <i>p</i> = 0.001) in severe COVID-19 patients.	NA	Warrants RCT

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
RDV	Goldman et al. [34]	RCT (NCT04292899)	USA, Italy, Spain, Germany, Hong Kong, Singapore, South Korea and Taiwan	397 patients (10-day course for 200 and 5-day course for 197)	IV	No significant difference between 5- or 10-day course	Nausea (9%), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%).	Warrants RCT
RDV	Garibaldi et al. [35]	Retrospective	USA	2309 patients (RDV = 158, RDV + CTS = 184 and C = 1957)	NA	Clinical improvement time is shorter in RDV group compared to control group.	Increased levels of liver enzyme or bilirubin ($n = 4$), kidney failure of unclear cause ($n = 2$), nausea ($n = 1$), epistaxis and tachycardia ($n = 1$), neck and mouth itching ($n = 1$)	Warrants further study
RDV	Tsuzuki et al. [36]	Observational study	Japan	269 patients (T = 74 and C = 195)	NA	No statistical significance was observed in fatality rate or length of hospital stay	Elevation of liver enzyme and rash ($n = 2$)	Warrants further study
RDV	Wang et al. [37]	RCT (NCT04257656)	China	237 patients (T = 158 and C = 79)	IV	No significant time difference for clinical improvement between the two groups (HR = 1.23, 95% CI = 0.87–1.75)	Adverse effects were reported for both groups; T = 102 (66%) and C = 50 (64%)	Numerical time reduction to clinical benefit was reported that warrants larger study
RDV	Spinner et al. [38]	RCT (NCT04292730)	USA, Europe, and Asia	596 patients (T: 10-day course for 197, 5-day course for 199, and C: 200)	IV	No statistically significant change between T and C ($p = 0.18$ by Wilcoxon rank sum test)	Nausea (10% vs. 3%), hypokalemia (6% vs. 2%), and headache (5% vs. 3%)	RCT is warranted
RDV + BCN	Kalil et al. [39]	RCT (NCT04401579)	USA, UK, Singapore, South Korea, Mexico, Japan, Spain, and Denmark	1033 patients (T = 515 and C = 518)	IV, oral	At 28-day fatality rate: T = 5.1% and C = 7.8% (HR for death = 0.65; 95% CI, 0.39 to 1.09).	Some common ADRs like hyperglycemia, anemia, decreased lymphocyte count, and acute kidney injury were present in both groups	The combination therapy was superior to only RDV.
RDV	Falcao et al. [40]	Observational cohort study	Lisbon, Portugal	149 patients (HCQ = 101 and RDV = 48)	Oral	ADRs were more significant the in case of HCQ (47.5%) than RDV (12.5%).	RDV group developed ADRs like hepatobiliary disorder (8.3%), acute renal failure, nervous system disorder, and others (2.1%).	Warrants larger sample size and follow-up study

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
RDV	Goldberg et al. [41]	Real-life observational	Israel	142 patients (T = 29 and C = 113)	IV	Reduced hospitalization in case of both non-intubated and intubated patients (3.1 vs. 1.4 days, respectively; $p > 0.05$)	NA	Warrants further study as sample size was small
RDV/CP/RDV + CP	Padilla et al. [42]	Retrospective observational study	California, USA	106 patients (RDV = 11, CP = 53, and RDV + CP = 42)	IV	Survival rate was higher with RDV alone than with combination therapy or CP alone.	NA	Warrants further study
FPV	Cai et al. [43]	Open level	China	80 patients (T = 35 and C = 45)	Oral	FPV showed significant improvement rate over the control (91.43% vs. 62.22%, respectively, $p = 0.004$).	T vs. C = 4 (11.43%) vs. 25 (55.56%), respectively; $p < 0.001$	Warrants RCT
FPV	Chen et al. [44]	RCT (ChiCTR2000030254).	China	240 patients (T = 120, C = 120)	NA	T showed shorter latency recovery from fever (difference: 1.70 days, $p < 0.0001$) and cough (difference: 1.75 days, $p < 0.0001$)	Increased serum uric acid 16 (13.79%) in FPVipiravir group, $p = 0.0014$	Adverse effects are mild and manageable.
FPV	Lou et al. [45]	RCT (ChiCTR2000029544).	China	30 patients (FPV = 10 Baloxavir marboxil = 10 and control = 10)	Oral	The viral loading was 77%, 70%, and 100% and median time was 14, 14, and 15, respectively after 14-day treatment.	Respiratory failure (14), triglyceride (20), liver function abnormality (18), rash (7), and diarrhea (4)	No proven benefit was observed either addition of baloxavir marboxil or FPV under the trial dosage.
FPV	<i>The New Indian Express</i> [46]	RCT	India	150 (FPV = 75 and control = 75)	Oral	Primarily FPV showed 28.6% numerical faster viral clearance	NA	Warrants RCT
FPV	<i>The Daily Star</i> [47]	RCT	Bangladesh	50	Oral	FPV showed 44% more viral clearance than placebo	No significant side effect was reported.	Warrants RCT
FPV	Ucan et al. [48]	Retrospective cohort	Turkey	144 (FPV + HCQ (early) = 48, FPV + HQ (late) = 48 and HQ = 48)	Oral	Early starting of FPV had an impact on PCR negativity and the progression of the disease.	Diarrhea, nausea, and vomiting	Needs RCT

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
FPV	Alamer et al. [49]	Retrospective	Saudi Arabia	457 (FPV = 234 and C = 223)	Oral	Improvement of discharge rate and less progression to ventilation; no effect on mortality in severe cases	Acute kidney injury, increased ALT, AST, bilirubin, cardiovascular effects, constipation, seizure, hypercalcemia, hyperphosphatemia, and hypermagnesemia	Warrants RCT
FPV	Zhao et al. [50]	RCT	China	55 (FPV = 36 and C = 19)	Oral	Improvement in virus shedding and CRP decreasing	Elevated AST and ALT, hyperuricemia, hypernatremia, diarrhea, and nausea.	Warrants RCT
FPV	Udwadia et al. [51]	RCT	India	150 patients (T = 75 and C = 75)	Oral	Median required time of reducing viral load between T and C was 5 days vs. 7 days and clinically median cure time was 3 days vs. 5 days, respectively	ADR: T vs. C = 36% vs. 8%, respectively	T showed significant improvement in time to clinical recovery
rhIFN- α	Meng et al. [52]	RTC (NCT04320238)	China	2944 patients (low risk = 2415 and high risk = 529)	Nasal drop	Observed negative clinical symptoms for pneumonia in both high- and low-risk groups after 28 days	Flu-like symptoms (burning pain and itching), allergic reactions (rash, nausea, chest distress, palpitation, and flushing)	Warrants RCT
IFN-alpha 2b	Pandit et al. [53]	RCT	India	40 (T = 20 and C = 20)	SC	Better clinical improvement (IFN = 95% and C = 68.42%) and viral shedding (IFN = 95% and C = 68%).	Respiratory distress, hypoxia, nausea, vomiting, mouth dryness, and headache	Further confirmatory studies needed
IFN-alpha 2b	Yu et al. [54]	Retrospective	China	1401 (T = 852 and C = 549)	Inhalation	Lower viral shedding time, improved clinical outcome	NA	Warrants RCT
IFN-lambda	Feld et al. [55]	RCT	Canada	60 (IFN = 30 and C = 30)	SC	Shortening of viral shedding duration, prevention of clinical deterioration, and acceleration of viral decline.	Confusion, rectal bleeding, pneumonia, and pulmonary embolism	Warrants larger studies
ARB	Wang et al. [56]	Cohort	China	69	NA	Improved hospital discharge rate and reduced mortality rate by 7.5%	NA	Study with larger samples needed

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
ARB	Lian et al. [57]	Retrospective	China	81 patients (ARB = 45 and control = 36)	NA	ARB showed better CT scores than control (IQR 7e14) vs. 8 (IQR 5e10), $p < 0.05$	5/45 (11%) ARB group and 3/36 (8%) control group showed digestive symptoms such as diarrhea and nausea ($p = 0.49$)	Warrants RCT
ARB	Zhu et al. [58]	Retrospective	China	50 patients (ARB = 16 and LPV/RTV = 34)	NA	After day 14, viral load was found between (ARB vs. LPV/RTV = 0% vs. 44.1%)	NA	ARB superior to LPV/RTV
ARB	Chen et al. [59]	Observational	China	62 patients (T = 42 and C = 20)	Oral	Test group reduced hospital stay duration more than control group	Nausea (test: $n = 7$, control: $n = 3$), diarrhea (test: $n = 2$, control: $n = 1$), and dizziness (test: $n = 2$, control: $n = 1$)	Warrants further study
ARB, oseltamivir	Liu et al. [60]	Retrospective cohort	China	504	NA	Both drugs reduced fatality rate	Nausea	ARB and oseltamivir reduced fatality rate.
ARB	Yang et al. [61]	RCT	China	164 patients (ARB = 82 and non-ARB = 82)	Oral	In the ARB group The uninfected rate was significantly higher than in the non-ARB group.	NA	Needs a multicenter cohort study
ARB	Zeng et al. [62]	Retrospective cohort	China	1019 (ARB = 788 and C = 231)	NA	ARB-treatment results in less in-hospital death for patients with severe and critical COVID-19.	NA	Warrants RCT
Oseltamivir	Tan et al. [63]	Cohort	China	333 patients (oseltamivir = 14, ARB = 277, corticosteroid = 15, HCQ = 8, LPV/RTV = 14)	NA	The oseltamivir group showed a significantly shorter hospital stay duration than the ARB, corticosteroids, and lopinavir/ritonavir groups.	NA	Oseltamivir prudently considered as a combination therapy
Oseltamivir	Moreno et al. [64]	Observational	Spain	2124 (T (early) = 529 and C (late) = 1595)	NA	Early treatment was associated with reduced mortality of critically ill patients infected with influenza pneumonia.	NA	Further studies needed

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
DRV/c	Deng et al. [65]	Retrospective	China	66 patients (DRV/c = 32 and control = 34)	Oral	DRV/c significantly shortened nucleic acid conversion duration from the onset of symptoms to admission.	Respiratory failure, upset stomach	Further studies needed
DRV/c	Kim et al. [66]	Retrospective	South Korea	110 patients (DRV-c group = 14 and control = 96)	NA	Overall, the DRV/c group showed a lower fatality rate than the control group (odds ratio (OR) 0.20, 95% CI = 0.04–0.89, $p = 0.035$).	NA	DRV-c showed significant survival benefit in critically ill Patients.
DRV/c	Chen et al. [67]	RCT (NCT04252274)	China	30 patients (DRV/c = 15 and control = 15)	Oral	The difference in negative PCR conversion rate in between two groups at day 7 was DRV/c vs. control = 9/15 (60.0%) vs. 7/15 (46.7%), respectively, $p = 0.72$.	In the DRV/c group, diarrhea (20%), anemia, elevated transaminase levels (13.3%), and renal dysfunction (13.3%) were observed.	5 days of DRV/c did not increase the rate of negative conversion vs. standard of care alone.
FPV + HQ	Guner et al. [68]	Retrospective	Turkey	824 (HQ = 604, FPV = 100 and FPV + HQ = 120)	Oral	No statistically significant difference between the three groups	NA	Warrants RCT
FPV + CQ	Dabbous et al. [69]	RCT	Egypt	96 (FPV = 48 and CQ = 46)	Oral	Improvement in hospital stay and need for mechanical ventilation in FPV groups	NA	Warrants a larger and diverse sample size
FPV vs. LPV/RTV	Kocayigit et al. [70]	Observational	Turkey	107 (FPV = 65 and RTV/LPV = 42)	Oral	Significantly shorter hospital stay in the case of FPV	Coinfection, ARDS, acute kidney disease, and MODS	Warrants larger sample
FPV vs. HCQ	Dabbous et al. [71]	RCT	Egypt	100 (FPV = 50 and HCQ = 50)	Oral	No significant difference in hospital stay	Elevated D-dimer and ferritin, cardiovascular complications	Warrants larger sample
FPV + IFN beta-1b	Khamis et al. [72]	RCT (NCT04385095)	Oman	89 patients (FPV + IFN beta-1b = 44 and HCQ = 45)	Oral	No significant difference in hospital stay between FPV and HCQ (7 vs. 7 days; $p = 0.948$), ICU transfer rate (18.2% vs. 17.8%; $p = 0.960$), or discharge rate (65.9% vs. 68.9%; $p = 0.764$), and fatality rate was 11.4% vs. 13.3%, respectively; $p = 0.778$	liver injury	No notable difference was found in clinical results between FPV + inhaled IFN beta-1b and HCQ.

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
LPV/RTV	Kim et al. [73]	Cohort	Korea	65 patients (T = 31, C = 34)	NA	No significant difference in time to clinical development between T and C groups (18 days vs. 21 days)	One serious ADR was detected for the T group and two serious ADRs were detected for the C group.	Warrants RCT
LPV/RTV, HCQ	Lee et al. [74]	Cohort	South Korea	72 patients (LPV/RTV = 45 and HCQ = 27)	Oral	The LPV/RTV group showed lower failure rate (41% vs. 2%; $p = 0.001$) and disease progression than the HCQ group (18% vs. 44%, respectively; $p = 0.03$).	Diarrhea, abnormal stools, abdominal pain, nausea, vomiting, and asthenia	LPV/RTV showed more efficacy than HCQ in improving clinical symptoms
LPV/RTV	Yu et al. [75]	Cohort	China	128	NA	The significant median period of viral load reduction time between with influenza and without influenza was 17.0 vs. 12.0 days, respectively; $p < 0.001$. Besides, the T group showed faster pneumonia resolution than the C group (37% vs. 1%; $p = 0.001$).	NA	Additional robust scientific studies with proper controls are needed.
LPV/RTV + SOC	Lecronier et al. [76]	Retrospective	Paris, France	80 patients (LPV/RTV + SOC = 20, SOC = 22, and HCQ + SCQ = 38 patients)	Oral	No significant difference at ventilator-free days at 28 days and mortality rate (at 14- and 28-days) in these 3 groups	NA	Warrants RCT
LPV/RTV + ARB	Lan et al. [77]	Retrospective	China	73 patients (T: LPV/RTV + ARB = 39 and C: LPV/RTV = 34)	Oral	The T group showed a 4.8% higher recovery rate and a 1.5-day shorter hospital stay than the C group.	NA	No benefit was observed between the two groups.
LPV/RTV + CQ	Gao et al. [78]	Retrospective	China	129 patients (LPV/RTV = 51, SOC = 59, and chloroquine = 19)	Oral	Neither LPV/RTV nor CQ improved prognosis or shortened the clinical course.	NA	Warrants RCT

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
LPV/RTV	Karolyi et al. [79]	Cohort	Austria	156 patients (T = 47 and C = 20)	IV	No significant difference in mortality rate (8.5% vs. 15%; $p = 0.418$), ICU admission rate (12.8% vs. 20%; $p = 0.47$), or hospital stay (11 days vs. 9 days, respectively; $p = 0.34$) was observed.	Diarrhea ($n = 7$) and liver enzyme elevation ($n = 7$)	Warrants RCT
LPV/RTV	Shi et al. [80]	Non-RCT (ChiCTR2000029400/ChiM-CTR2000002940).	China	60 patients (LPV/RTV = 20, Huashi Baidu Formula + LPV/RTV = 20, Huashi Baidu Formula = 20)	Oral	No significant difference was observed for clinical remission rate between the 3 groups (95% (19/20), 100% (20/20), and 100% (20/20)).	NA	Warrants larger RCT
LPV/RTV	Cao et al. [81]	RCT (ChiCTR2000029308)	China	199 patients (T = 99 and C = 100)	Oral	No significant difference between LPV/RTV and SOC was observed in clinical improvement or mortality rate.	GI ADRs were more common in the treatment group.	No significant difference was observed between the two groups.
LPV/RTV, ARB	Li et al. [82]	RCT (NCT04252885)	China	44 patients (LPV/RTV = 21, ARB = 16, and SOC = 7)	Oral	No significant difference between groups in antipyresis, cough alleviation, or improvement of chest computed tomography (CT)	12 and 5 patients were suffering from ADRs in the LPV/RTV and ARB groups, respectively.	No significant benefit was observed among these three groups.
LPV/RTV + RBV + IFN beta-1b	Hung et al. [83]	RCT (NCT04276688)	China	127 (combination group 86 and control (LPV/RTV) = 41)	Oral, SC	The combination group showed a significantly shorter recovery time than the control (7 days vs. 12 days, respectively; HR = 4.37, 95% CI = 1.86–10.24; $p = 0.0010$).	Diarrhea (52 (41%)), fever (48 (38%)), nausea (43 (34%)), and raised alanine transaminase level (18 (14%))	Early triple combination therapy showed lower recovery time with safety than only LPV/RTV.
LPV/RTV + IFN-a	Huang et al. [84]	RCT (ChiCTR2000029387)	China	101 patients (LPV/RTV + IFN- α = 36, RBV + IFN- α = 33, and LPV/RTV + RBV + IFN- α = 32)	Oral	No statistically significant differences in viral clearance among these 3 groups (LPV/RTV + IFN-a vs. RBV + IFN-a vs. RBV + LPV + IFN-a = 12 days vs. 13 days vs. 15 days, respectively; $p = 0.23$)	Adverse gastrointestinal events were higher for the LPV/RTV + RBV + IFN-a group than the LPV/RTV + IFN-a and RBV + IFN-a groups	No significant difference was observed among the three groups.

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
LPV/RTV	RECOVERY Collaborative Group [85]	RCT (NCT04381936)	UK	5040 patients (LPV/RTV = 1616 and standard of care = 3424)	Oral	No significant difference at 28-day fatality rate (LPV/RTV vs. SOC = 23% vs. 22%, respectively; $p = 0.60$)	NA	The treatment is not effective for COVID-19.
LPV/RTV + recombinant IFN beta-1b	Arabi et al. [86]	RCT (NCT02845843)	Saudi Arabia	95 patients (LPV/RTV + recombinant IFN beta-1b = 43 and placebo = 52)	Oral, SC	Intervention therapy against MERS-CoV led to lower fatality rate (RR = 0.19; 95% CI = 0.05 to 0.75) than placebo	Serious ADRs: Intervention (4 (9%)) and placebo (10 (19%))	Further study with larger sample size
CQ+ LPV/RTV	Sevilla-Castillo et al. [87]	Retrospective	Mexico	61 (LPV/RTV = 27, CQ = 11, combination = 17 and C = 6)	Oral	Both the drugs were ineffective in COVID treatment; combination therapy enhanced mortality.	Increase in lactate dehydrogenase and ferritin	Warrants further investigation
IFN beta 1b + LPV/RTV + RBV vs. FPV	Malhani et al. [88]	Cohort	Saudi Arabia	222 (IFN triple therapy = 68 and FPV = 154)	Oral, SC	IFN-based triple therapy decreased the mortality rate in non-critical patients.	Nausea and diarrhea	Warrants RCT
LPV/RTV	Lepage et al. [89]	Retrospective	Canada	12	Oral	Trough concentration is higher when an HIV dose regimen is used; dose tapering might be needed to avoid risk in COVID-19 patients.	GI symptoms, electrolyte imbalance, liver enzyme disturbance, and TG elevation	Warrants RCT
LPV/RTV+ HCQ	Schneider et al. [90]	Retrospective	Germany	79 (Non-ICU-LPV/RTV+ HCQ = 14 and C = 14; ICU-LPV/RTV = 30 and 4C = 21)	Not mentioned	Triple therapy may cause elevated acute kidney injury in non-severe COVID patients.	Slight hematuria and proteinuria	Warrants RCT
IFN-k + TFF2 + SOC	Fu et al. [91]	RCT (ChiCTR2000030262)	China	80 patients (experimental group = 40 and control group = 40)	inhalation	The experimental group exhibited significantly shorter days in viral RNA (-ve) conversion than the control group (3.8 vs. 7.40 days, respectively).	No discomfort or complication was reported.	The experimental combination with SOC is safe and superior to SOC alone.

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
rSIFN vs. traditional IFN-alpha	Li et al. [92]	RCT	China	94 (rSIFN = 46 and IFN-alpha = 48)	Nasal (Nebulization)	Shortened the clinical improvement time (rSIFN vs. INF-alpha = 11.5 days vs. 14 days, respectively), clinical improvement rate (rSIFN = 93.5%, IFN-alpha = 77.1%), radiological improvement time (rSIFN = 8 days, IFN-alpha = 10 days), and viral shedding time (rSIFN = 7 days, IFN-alpha = 10 days)	Decreased appetite	rSIFN was associated with shorter time of clinical improvement. However, a broader-range trial is needed.
IFN- alpha + RBV	Li et al. [93]	Retrospective cohort	China	2037 (RBV = 840, IFN-alpha = 214, RBV + IFN-alpha = 227, and C = 756)	NA	No significant difference in mortality rate between the two groups	Decreased hemoglobin and increased uric acid	Should avoid this combination in the treatment of COVID-19
IFN-beta 1a vs. IFN-beta 1b	Darazam et al. [94]	RCT	Iran	60 (IFN-beta 1a = 20, IFN-beta 1b = 20, and C = 20)	SC	Improved time to clinical improvement in IFN-beta 1a group	Liver injury, ARDS	Warrants larger studies
ARB + LHQW	Fang et al. [95]	Cohort	China	162	Oral	Significantly shortened nucleic acid negativity, improved chest CT, and reduced hospital stay duration	NA	Warrants RCT
ARB + LPV/RTV	Wen et al. [96]	Cohort	China	178	NA	Significant difference in proportion of deterioration changing from mild/moderate to severe/critical type at day 7 was found	ADRs were higher than the SOC group.	Warrants larger studies
ARB + LPV/RTV	Deng et al. [97]	Cohort	China	33 patients (ARB + LPV/RTV = 16 and LPV/RTV = 17)	Oral	Observed significant difference in SARS-CoV-2 negativity between ARB + LPV/RTV and LPV/RTV groups at day 7 (75% vs. 35%; $p < 0.05$) and day 14 (94% vs. 52.9%, respectively)	Digestive upset (43.7%), such as mild diarrhea and nausea	Warrants RCT

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
ARB + Shufeng Jiedu capsules	Chen et al. [98]	Cohort	China	200 (experimental = 100 and control = 100)	Oral	The experimental group showed significantly more efficacy in pneumonia resolution than the control group ($p < 0.05$).	Nausea, allergic reaction, abdominal pain, and diarrhea were common for both groups.	Warrants RCT
ARB + Shufeng Jiedu capsules	Qu et al. [99]	Observational	China	70 patients (ARB + Shufeng Jiedu capsules = 40 and ARB group = 30)	Oral	The combination group (ARB + Shufeng Jiedu capsules) reduced negative conversion time significantly more than the ARB group ($p < 0.05$).	NA	The combination therapy was better than the ARB alone.
ARB + LQ granules	Yu et al. [100]	Observational	China	295 patients (observation group = 147 and control group = 14)	Oral	Effective rate was significantly higher in observation group than control group (80.95% vs. 64.86%, respectively)	NA	Warrants further intensive study
ARB + moxifloxacin	Xi et al. [101]	Cohort	China	94	NA	Treatment with ARB + moxifloxacin reduced viral load and inflammation.	NA	Warrants further clinical verification
ARB vs. CQ	Huang et al. [102]	Cohort (ChiCTR2000030931)	China	27 patients (ARB = 11, CQ = 10, and LPV/RTV = 6)	NA	The median viral shedding interval for LPV/RTV and CQ were 13 and 5 days, respectively. Hospitalization duration was in ARB (11.7 ± 3.7 days; $p < 0.001$) and CQ (9.3 ± 1.8 days, respectively; $p < 0.001$)	20% of patients from the CQ group (nausea, vomiting, dysphoria, or blurred vision), 9.1% of the ARB group, and 50% of the LPV/RTV group had diarrhea.	ARB and CQ reduced hospital stay and hospitalization expenses.
ARB + IFN-a2b	Xu et al. [103]	Non-RCT	China	141	Oral	No significant difference was reported in viral load clearance and hospital stay duration between ARB + IFN-a2b and IFNa-2b	NA	Warrants RCT
ARB vs. KALETRA	Nojomi et al. [104]	RCT (IRCT20180725040596N2)	Iran	100 patients (ARB = 50 and KALETRA = 50)	Oral	ARB significantly reduced hospital stay duration compared to the KALETRA arm (7.2 vs. 9.6 days, respectively; $p = 0.02$).	Nausea and vomiting	Warrants more studies with larger sample size

Table 1. Cont.

Drug	Reference	Study Type	Country	n	ROA	Results	ADR	Interpretation
ARB + HCQ	Ghaderkhani et al. [105]	RCT	Iran	56 patients, 3 patients left from ARB group; ARB (n = 28) and control (n = 25) arms	NA	After 7 days, the ARB + HCQ group showed significantly faster recovery in dry cough (p = 0.001), weakness (p = 0.004), gastrointestinal symptoms (p = 0.043), and shortness of breath (p = 0.001) than the control group.	Dermatitis, GI symptoms (nausea and diarrhea), jaundice, and neurological symptoms were not observed in any of the patients after 14 days.	The combination group showed a better effect in the recovery process.
ARB vs. CQ	Li et al. [106]	Retrospective	China	62 (ARB = 42 and CQ = 20)	NA	Length of hospital stay was significantly lower for the ARB than the HCQ group.	Vomiting, hepatic function impairment, and ALT elevation	Warrants RCT
Oseltamivir + antibacterial agents (levofloxacin + garenoxacin)	Chiba et al. [107]	Cohort	Japan	16 patients	Oral	Early treatment with oseltamivir shortened fever duration time compared to the late treatment (31 ± 21 h vs. 94 ± 38 h, respectively; p < 0.001).	Mild side effects were present.	Early use of oseltamivir might reduce fever duration.
DRV/RTV + HCQ	Meriglier et al. [108]	Cohort	France	46 patients (HCQ + DRV/RTV = 25 and HCQ + LPV/RTV = 21)	Oral	Combination therapy led to severe illness.	ECG abnormalities (n = 4), repolarization disorder (n = 3), conduction disorder (n = 1), diarrhea grade I/II (n = 8), and hepatic enzyme increased (n = 1)	Concomitant use was not safe.
INF beta-1a vs. medications of national protocols	Davoudi-Monfared et al. [109]	RCT (IRCT20100228003449N28)	Iran	81 (T = 42 and C = 39)	SC	Significantly improved the discharge rate and decreased the 28-day mortality rate.	For the IFN beta-1a group: IFN-related injection reactions (19.04), neuropsychiatric problems (9.52%)	Needs more extensive study
Novaferon + LPV/RTV	Qu et al. [110]	Case-control study	China	170 (male = 81 and female = 89)	NA	Novaferon + LPV/RTV exerted a lower duration of hospital stay and negative nucleic acid conversion compared to LPV/RTV or combination with IFN or ARB.	NA	Novaferon + LPV/RTV may have better efficacy than these control groups. Warrants RCT

3.2. Favipiravir (FPV)

Favipiravir (FPV, T-705, 6-fluoro-3-hydroxypyrazine-2-carboxamide), a pyrazine analog, is another broad-spectrum RNA-dependent RNA polymerase (RdRp) enzyme inhibitor that has been used in an extended pandemic platform to treat patients with COVID-19 in various countries around the world [111,112].

Cai et al. [43] performed an open-level, controlled trial on 80 COVID-19 patients to evaluate the safety and efficacy of FPV in comparison with lopinavir-ritonavir (LPV/RTV) as a control. In this study, 35 patients were subjected to FPV treatment (1600 mg on the first day and 600 mg twice daily for the next 19 days), 45 patients to LPV/RTV treatment (400 mg/100 mg twice daily), and both groups also received 5 million units of interferon (IFN)- α aerosol inhalation twice daily. In chest imaging, computed tomography (CT) demonstrated a substantial improvement rate with FPV compared to the LPV/RTV group (91.43% vs. 62.22%, respectively; $p = 0.004$) with several adverse consequences. FPV displayed relatively better therapeutic upshots in viral load reduction along with slower disease progression in this open-level controlled study. A randomized, multicenter, open-level phase 3 trial was undertaken on 150 patients (FPV = 75 and control = 75) with mild to moderate severity of COVID-19 in India by Glenmark Pharmaceuticals. After 4 days, FPV exhibited statistically noteworthy upshots in refining clinical symptoms compared to the control group (69.8% vs. 44.9%, respectively) [46]. Recently, a clinical trial on 50 patients with COVID-19 in Bangladesh (Dhaka trial) was accomplished, where FPV demonstrated significant viral clearance following 10 days of treatment (FPV = 96% and placebo = 52%) with a good safety profile [47]. Another retrospective cohort study conducted by Alamer et al. [49] showed that FPV reduced the median time of hospital discharge (FPV and SOC = 10 days vs. 15 days, respectively) and was associated with less progression to mechanical ventilation. However, the drug did not significantly influence the mortality rate of severe cases [49]. Zhao et al. [50] conducted a multicenter, open-labeled randomized trial on 55 SARS-CoV-2 re-positive patients (FPV = 36 and SOC = 19). They revealed that the FPV shortened the duration of viral shedding and significantly decreased C-reactive protein (CRP) levels compared to the control group.

An additional study performed on 150 patients with mild to moderate COVID-19 (FPV and control = 1:1) reported that the drug significantly reduced the required median time to cessation of viral termination (5 days vs. 7 days, respectively) and clinical cure time (3 days vs. 5 days, respectively). However, the FPV group of patients showed more adverse drug reactions compared to the control group (36% vs. 8%, respectively) [51]. Another study reported in Turkey that a 31-year-old female receiving FPV treatment developed some neurotic disorders that were suspected to be caused by the drug [112]. Despite possessing excellent therapeutic profiles, FPV showed embryotoxic and teratogenic effects. Therefore, the Japanese Drug Safety Bureau provided strong warnings regarding the use of FPV in pregnant women [113]. Additionally, Kaur et al. [114] assessed the adverse drug events (ADEs) of FPV by analyzing the WHO pharmacovigilance data set and concluded that FPV reduced inflammatory markers as well as offered clinical improvement for critically ill patients.

Moreover, an open-level, randomized control trial conducted by Khamis et al. [72] found no significant difference in therapeutic output of the drug plus inhaled interferon beta-1b in the treatment of hospitalized moderate-to-severe COVID-19 patients. Chen et al. [44] performed an open-level, multicenter, and randomized controlled trial on 240 patients (FPV = 120, Arbidol (ARB) = 120) with COVID-19 and reported that FPV showed shorter latency recovery from fever and cough. Additionally, Lou et al. [45] conducted a randomized trial (ChiCTR2000029544) on 30 patients (baloxavir marboxil = 10, FPV = 10, and control = 10) with COVID-19. After the 14 days of the experiment, the percentage of cessation of viral shedding was 70%, 77%, and 100%, respectively. Due to lack of time from the onset of symptoms to randomization, the baloxavir marboxil, and control groups did not confer clinical benefits against SARS-CoV-2 compared to the FPV group. Another retrospective study reported that the patients who received hydroxy-

chloroquine (HCQ) alongside early treatment of FPV showed more PCR negativity and slower progression of the disease [48]. However, Dabbous et al. [69] reported no significant difference among HCQ, FPV, and their combination therapy groups regarding beneficial effects against COVID-19.

3.3. Interferons (IFNs)

IFNs (alpha, beta, and gamma) are naturally occurring groups of cytokines that serve as natural barriers against foreign viruses, bacteria, mitogens, and tumor cell infections. When they are bound to the target receptors, a variety of genes become activated, which accounts for antiviral and antiproliferation, and immunomodulation activities [115]. The US FDA approved IFN- β to treat multiple sclerosis and hepatitis B and C infections [116]. A deficiency state of interferon might elicit the SARS-CoV-2 infection, and several clinical trials have been started since the inception phase of the pandemic to evaluate the safety and efficacy of IFNs against COVID-19 [117].

An open-label prospective clinical trial was conducted by Meng et al. [52] to investigate the safety and efficacy of rhIFN- α (recombinant human interferon-alpha) nasal drops with or without thymosin- α 1 on medical professionals. The authors concluded that the rhIFN- α strictly protected medical staff with the augmented safeguards. A randomized multicenter clinical trial was conducted by Li et al. [92] to evaluate the efficacy of recombinant super compound-interferon (rSIFN-co) with traditional IFN in COVID-19 treatment, and the rSINF group showed better clinical improvement time (rSIFN = 11.5 days, IFN-alpha = 14 days), clinical improvement rate (rSIFN = 93.5%, IFN-alpha = 77.1%), radiological improvement time (rSIFN = 8 days, IFN-alpha = 10 days), and viral shedding time (rSIFN = 7 days, IFN-alpha = 10 days). Another randomized control trial was reported wherein IFN-alpha 2b exerted greater efficacy in the duration of hospitalization and viral clearance [53]. In another retrospective study in China on 1401 patients with COVID-19 (T = 852 and C = 549), Yu et al. [54] showed improved viral clearance and decreased hospital stay by using IFN-alpha 2b. In addition, IFN-lambda resulted in accelerated viral decline and better clinical improvement in a randomized control trial [55]. Additionally, Yuan et al. [118] assessed that the combination therapeutic regimens of IFN- α with LPV/RTV or ribavirin or both options displayed favorable responses in contrast to COVID-19 infection. During the treatment of 77 hospitalized SARS-CoV-2-infected patients with IFN- α 2b with or without arbidol (ARB), Zhou et al. [119] found a reduced duration of viral loading in the upper respiratory tract as well as less duration of inflammatory markers in the blood. In a multicenter retrospective cohort study, Wang et al. [120] exhibited that early treatment with IFN- α 2b decreased hospital fatality, although late treatment with IFN was associated with higher fatality in the case of patients with COVID-19.

Another randomized controlled trial (IRCT20100228003449N28) on 81 patients with severe COVID-19 [109] assessed the efficacy and safety of IFN beta-1a compared with a control group ($n = 39$; taking medications only according to national guidelines). Although the primary result displayed no significant difference between the IFN and the control groups ($p = 0.95$) in time to clinical response, early administration of IFN beta-1a greatly improved the discharge rate (odds ratio (OR), 2.5; 95% confidence interval (CI), 1.05 to 6.37) on day 14 and decreased the 28-day mortality rate (treatment vs. control = 19% vs. 43.6%, respectively; $p = 0.015$). Fu et al. [91] conducted another randomized, open-level clinical trial (ChiCTR2000030262) on 80 patients (experimental group = 40 and control group = 40) to evaluate the safety and efficacy of the combination of IFN-k plus TFF2 with standard of care (SOC) and SOC alone. In comparison between the two groups, the experimental group shortened the viral RNA negative conversion time more than the control group (3.80 days, 95% CI = 2.07 to 5.53 vs. 7.40 days, 95% CI = 4.57 to 10.23, respectively; $p = 0.031$). Li et al. [93] compared the efficacy among IFN-alpha, ribavirin (RBV), and the combination (IFN-alpha = 240, RBV = 814, combination = 227, and C = 756) in a retrospective cohort study, and no significant clinical improvement was observed in the combination group. Therefore, the authors suggested that this combination needs to be avoided during the

treatment of COVID-19. In another randomized controlled clinical trial ($n = 60$; IFN β 1a = IFN β 1b = control = 20), Darazam et al. [94] found that IFN β -1a had a significant difference in time to clinical improvement compared to the control group. In contrast, INF β -1b exerted no significant influence on time to clinical improvement.

3.4. Lopinavir-Ritonavir (LPV/RTV)

Lopinavir (LPV) is usually prescribed for the prevention of human immunodeficiency virus (HIV) as well as, previously, SARS-CoV and MERS-CoV infections, in combination with a lower dose of a ritonavir (RTV) booster. Mechanistically, LPV acts as a peptidomimetic inhibitor of the HIV-1 protease enzyme, whereas RTV plays a key role as a pharmacokinetics promoter of LPV by slowing down its hepatic metabolism of the CYP3A4 enzyme, and thus increasing the plasma concentration and plasma half-life of LPV [121,122]. Because of its potential effect on viral loading at the cellular stage, initial therapy of LPV/RTV in COVID-19 demonstrated a decrease in steroid usage and nosocomial infections depending on the SARS and MARS experiences [123].

In a retrospective cohort study, Lee et al. [74] compared the clinical improvement of LPV/RTV with HCQ in patients with mild to moderate COVID-19. In this study, the clinical failure rate was more common in the HCQ group than in the LPV/r group (41% (11/27) vs. 2% (1/45), respectively; $p = 0.001$) and the disease progression rate was 44% (12/27) and 18% (8/45), respectively ($p = 0.030$). Finally, the authors [74] concluded that LPV/RTV was superior to HCQ in preventing the disease progression to severe COVID-19. Another cohort study carried out by Yu et al. [75] measured the effect of LPV/RTV on 128 enrolled COVID-19 patients divided into influenza A/B coinfecting ($n = 64$) and non-infected ($n = 64$) groups. In this retrospective study, LPV/RTV displayed a significant difference in the median duration of viral shedding time in patients with influenza compared to non-influenza (17.0 vs. 12.0 days, respectively; $p < 0.001$). Among the patients with coinfecting with influenza, those who were treated with LPV/RTV showed pneumonia resolution within two weeks after the onset of symptoms (37% vs. 1%, respectively; $p = 0.001$). Another open-level randomized controlled platform clinical trial [85] on 5040 hospitalized COVID-19 patients (SOC = 3424 and LPV/RTV = 1616) presented no significant difference in the 28-day fatality rate (LPV/RTV vs. SOC = 23% vs. 22%, respectively rate ratio = 1.03, 95% CI = 0.91–1.17; $p = 0.60$). In this study, LPV/RTV did not improve clinical outcomes by minimizing hospital stay, mechanical ventilation, or mortality rate. A retrospective study was conducted to observe whether the conventional dose of LPV/RTV used for HIV can be used in COVID-19 patients; it turns out dose tampering is a mandatory act to use the drug for the latter purpose [89]. Cao et al. [74] conducted a randomized, controlled, open-label clinical trial (ChiCTR2000029308) on 199 patients (LPV/RTV = 99 and SOC = 100). Even though clinical improvement was observed (hazard ratio (HR) = 1.13, 95% CI = 0.95, 1.80), no significant difference was found in mortality rate at day 28 (LPV/RTV vs. SOC = 19.2% vs. 25%, respectively, absolute difference: -5.8 , 95% CI = -17.3 , -5.7).

Moreover, Kim et al. [73] conducted a retrospective study on 65 patients (LPV/RTV = 31, HCQ = 34) with mild to moderate COVID-19, and reported that LPV/RTV exhibited shorter viral clearance time (adjusted hazard ratio (aHR), 2.28; 95% confidence interval (CI), 1.24 to 4.21) than HCQ treatment. However, no significant difference in clinical improvement was observed between the groups (median: 18 days vs. 21 days, respectively). In contrast, lymphopenia and hyperbilirubinemia were more frequent in the LPV/RTV group than the control group. Lecronier et al. [76] conducted a retrospective study on 80 patients with COVID-19 divided into three groups (SOC = 22, LPV/r + SOC = 20, and HCQ + SCQ = 38 patients). At day 28, treatment escalation was observed (SOC = 41%, LPV/r + SOC = 50%, HCQ + SOC = 39%; $p = 0.567$) and no substantial difference was observed between these three groups in 28 ventilator-free days and the 14-day fatality rate.

In a study conducted by Lan et al. [77], the patients receiving lopinavir-ritonavir or an arbidol combination (LPV/RTV + ARB) displayed a 4.8% higher remedy rate and 1.5-day hospital stay compared to those who received LPV/RTV therapy only. Another retro-

spective study [78] conducted on a total of 129 non-severe COVID-19 patients (SOC = 59, LPV/RTV = 51, and chloroquine, CQ = 19) found no significant difference in the improvement of prognosis of disease or shortening the clinical course. Similarly, in another cohort study on 156 hospitalized patients (median age, 72 years (IQR: 55.25–81)) with severe COVID-19 to compare the safety and efficacy of LPV/RTV ($n = 47$) with HCQ ($n = 20$), Karolyi et al. [79] observed no significant differences in mortality rate (8.5% vs. 15%, respectively; $p = 0.418$), ICU admission rate (12.8% vs. 20%, respectively; $p = 0.47$), or hospital stay (11 days vs. 9 days, respectively; $p = 0.34$).

In a non-randomized controlled trial, LPV/RTV showed a clinically effective and safety index for the enrolled COVID-19 patients. Here, 60 patients were involved in three groups (LPV/RTV = 20, Huashi Baidu Formula + LPV/RTV = 20, Huashi Baidu Formula = 20) and their clinical remission rates were 95% (19/20), 100% (20/20), and 100% (20/20), respectively. No significant differences were found among these three groups. However, these results urgently need to be confirmed further by well-designed prospective double-blinded randomized control clinical trials [80]. In addition, Li et al. [82] conducted a randomized control trial (NCT04252885) on 86 patients (LPV/RTV = 34, ARB = 35, and control = 17) with mild to moderate COVID-19. The difference in the median time of the negative conversion rate of SARS-CoV-2 nucleic acid, antipyresis, cough alleviation, and improvement of chest computed tomography (CT) was not significant ($p > 0.05$).

Hung et al. [83] conducted a randomized, open-level, prospective, multicenter, phase II, controlled trial (NCT04276688) on 127 (combination group = 82 and control group = 41) hospitalized patients with COVID-19. The trial, randomized at a 2:1 ratio for 14 days, involved triple combination group therapy named LPV/RTV (400 mg/100 mg twice daily), IFN beta-1b (3 doses of 8 million IU on alternate days), and ribavirin (400 mg twice daily), and the control group was LPV/RTV (400 mg/100 mg twice daily). The required median time for negative COVID-19 results from the day of the onset of treatment for the combination group and control group was 7 days (IQR = 5–11) and 12 days (IQR = 8–15), respectively (hazard ration (HR) 4.37 (95% CI 1.86–10.24), $p = 0.0010$). Triple combination therapy depicted significantly lower recovery median time together with greater safety and efficacy than the control group with no mortality during the study. Huang et al. [84] performed an open-level, randomized, single-center, prospective clinical trial (ChiCTR2000029387) on patients with mild to moderate severity of COVID-19 divided into three groups (ribavirin (RBV) + I-a: LPV/RTV + IFN-a: ribavirin + LPV/r + IFN-a = 1:1:1). In this analysis, the median time of positive-to-negative conversion of SARS-CoV-2 nucleic acid in LPV/RTV + IFN-a, RBV + IFN-a, and RBV + LPV + IFN-a groups was 61%, 51.5%, and 46.9%, respectively ($p = 0.23$). Though this result showed no significant difference among these three groups, the combination therapy of RBV and LPV/RTV offered a significant increase in gastrointestinal adverse consequences. So, combination therapy of RBV and LPV/r should not be relied on in COVID-19 patients. Arabi et al. [86] conducted a randomized, placebo-controlled, double-blinded adaptive clinical trial (NCT02845843) on 95 patients infected with MERS-CoV (intervention (LPV/RTV + recombinant IFN beta-1b) = 43 and placebo = 52) in nine sites in Saudi Arabia. In this analysis, the primary outcome at day 90 that accounted for the adaptive design yielded a risk difference of 19%. Intervention treatment contributed to a reduced probability of fatality (relative risk 0.19; 95% CI, 0.05 to 0.75) than the placebo with serious adverse responses, such as increased levels of liver enzymes.

A retrospective analysis found that both CQ and LPV/RTV showed ineffectiveness in the case of severe COVID-19, whereas a combination of them enhanced mortality [87]. Another cohort study of non-critical COVID-19 patients receiving FPV ($n = 154$) and triple therapy (INF-beta 1b + RBV + LPV/RTV) showed that the triple therapy decreased mortality [88]. Additionally, Qu et al. [110] assessed the therapeutic efficacy of LPV/RTV alone or in combination with IFN, novaferon, and arbidol against 170 COVID-19 patients (male = 81 and female = 89), which resulted in the promising favorable consequence of LPV/RTV combined with novaferon than LPV/RTV alone or any combinations (LPV/RTV + IFN or

LPV/RTV + IFN + arbidol, LPV/RTV + IFN + novaferon). Choi et al. [124] reported no significant difference in viral shedding between HCQ and LPV/RTV groups. A comparative randomized clinical trial between sofosbuvir/daclatasvir (SFV/DCV) and LPV/RTV was carried out where only the discharge rate was better in the LPV/RTV group; better survival rate and fewer complications were shown in the SFV/DCV group [125]. Similarly, Lepage et al. [89] and Schneider et al. [90] conducted retrospective studies and found several preliminary results that warrant well-designed and more extensive randomized controlled clinical trials.

3.5. Arbidol (ARB)

Umifenovir, popularly known as arbidol (ARB), is a drug of choice in the prophylactic treatment of the influenza virus. It has recently been recommended against COVID-19 due to its therapeutic benefits against the SARS-CoV-2 infection [126]. From the outset, Wang et al. [127] showed that ARB had profound efficiency in inhibiting SARS-CoV-2 infection by interfering with virus entry (~75% inhibition) to host cells and post-entry (~55% inhibition) by blocking intracellular vesicle trafficking. Several clinical studies have been started to investigate its safety and efficacy against COVID-19.

Zhang et al. [128] performed a retrospective cohort study on 66 members in 27 families and 124 health care workers who were close to COVID-19 patients. The study reported that ARB could minimize the infection risk of SARS-CoV-2. Likewise, a cohort study explained that ARB treatment progressed the hospital discharge rate and decreased the mortality rate by 7.5%. [56]. In addition, Xu et al. [129] described that ARB accelerated the viral clearance and is clinically effective for COVID-19 infection. Moreover, prophylactic therapy of ARB could reduce the incidence of COVID-19 infection but not the hospitalization rate in health care providers [61]. Additionally, a retrospective cohort study (ChiCTR2000030931) carried out by Huang et al. [102] noted that ARB reduced the viral shedding interval and declined the hospitalization duration rate. In another retrospective cohort study, ARB showed decreased fatality rate in severe COVID-19 patients [62]. Additionally, Deng et al. [97] reported that the combination therapy of ARB with LPV/RTV demonstrated significant efficiency compared to LPV/RTV monotherapy in terms of viral clearance at the 7th day (75% vs. 35%, respectively; $p < 0.05$). Furthermore, another retrospective cohort study [98] reported that the combination therapy (Shufeng Jiedu capsules + ARB) had notable clinical safety, efficacy, and a higher recovery time compared to the control therapy.

Moreover, a retrospective non-randomized multicenter cohort study [103] concluded that ARB/IFN-2b could be prescribed to ameliorate COVID-19 pneumonia in mild patients, though the therapy was ineffective at accelerating virus clearance. In addition, an open-label controlled clinical trial [104] observed that ARB significantly improved clinical and laboratory conditions compared to LPV/RTV. Additionally, Zhu et al. [58] recommended that ARB monotherapy has more effectiveness in viral clearance compared to LPV/RTV. Another study [59] demonstrated that adjuvant therapy combined with ARB might relieve fever and accelerate the recovery time. Moreover, another study [100] found faster curative efficacy by using a combined treatment of ARB along with Lianhua Qingwen granules (80.95% vs. 64.86%, respectively; $p < 0.05$). In addition, studies have shown that ARB and moxifloxacin therapy in severe COVID-19 patients is correlated with lowering the viral load and fatal inflammation [101]. Another retrospective cohort study was conducted to compare the efficacy of ARB, LPV/RTV, and oseltamivir, wherein the ARB group dominated due to its lower fatality rate and higher viral clearance [60]. Furthermore, Li et al. [106] concluded that ARB was superior to HCQ in terms of duration of hospital stay and SARS-CoV-2 negative conversion. Moreover, a randomized control trial proved the higher benefit in using ARB over HCQ, as it was responsible for the improvement of clinical symptoms and recovery rate [105].

A retrospective cohort study conducted by Fang et al. [95] manifested that combined medication (traditional Chinese medicine called Lianhuaqingwen + ARB) did not accelerate the recovery of severe COVID-19 patients. Similarly, a retrospective observational

study (ChiCTR2000030391) [99] concluded that the combined medication (ARB + Shufeng Jiedu Capsules) did not show any noticeable effect compared to a single administration. Another study conducted by Yadegarinia et al. [130] assessed that ARB could not cure severely infected patients, but it was effective in mild to moderate conditions. Similarly, Chen et al. [131] reported that the antiviral medications did not shorten the clearance of viral RNA in acute patients. Moreover, Wen et al. [96] found that ARB combined with LPV/RTV could not improve clinical condition and did not reduce the time to convert the nucleic acid of SARS-CoV-2 to negative. Likewise, Lian et al. [57] discovered that ARB might not accelerate viral clearance, and treatment led to a longer hospitalization rate compared to standard care. Furthermore, a randomized controlled multicenter trial (ChiCTR2000030254) [44] concluded that ARB did not show any notable recovery rate at day 7 (FPV = 71/116 and ARB = 62/120; $p = 0.1396$). So far, a variety of randomized phase IV clinical studies, for instance, NCT04260594, NCT04255017, NCT04254874, NCT04350684, and so on, are now under investigation to evaluate the safety and efficacy of ARB combination therapy or a standard/control therapy.

3.6. Oseltamivir

Oseltamivir, commonly known as Tamiflu, is a first-line antiviral treatment formerly used to treat and prevent flu A and flu B. It inhibits the distribution of neuraminidase on the surface of the influenza virus in the human body [132,133]. An initial study in Wuhan reported that several patients were treated with oseltamivir as an empirical therapy before SARS-CoV-2 was detected, but no positive result was found [134]. Although oseltamivir monotherapy has not shown any significant effect against COVID-19 [135], numerous clinical trials are still taking it into consideration to evaluate the efficacy of oseltamivir against COVID-19 infection [136].

An observational study showed that early exposure to oseltamivir significantly reduced ventilation duration, hospital/ICU stay, and overall fatality rate compared to late exposure among critically ill patients with influenza pneumonia [64]. Tan et al. [63] conducted a retrospective analysis on 333 patients with COVID-19 and reported that oseltamivir significantly reduced hospital stay ($p = 0.0096$) over other groups (LPV/RTV, ARB, corticosteroids). This trial also showed that a combined treatment of oseltamivir with hydroxychloroquine might be prudent in patients with COVID-19. Chiba et al. [107] performed another study that included 16 healthcare providers suspected of having COVID-19 and their cohabitation families without hypoxia. The authors concluded that early administration of oseltamivir plus antibacterial therapy might reduce the duration of fever in outpatients suspected to have COVID-19 without hypoxia.

On the other hand, a real-world observational study [137] performed on 395,343 patients led to the observation that oseltamivir is associated with increased mortality in the general population (HR = 1.72, 95% CI: 1.61–1.84), ambulatory patients (HR = 4.79, 95% CI: 4.01–5.75), non-critical patients (HR = 2.05, 95% CI: 1.88–2.23), and pregnant patients (HR = 8.35, 95% CI: 1.77–39.30), as well as hospitalized (HR = 1.13, 95% CI: 1.01–1.26) and critical patients (HR = 1.22, 95% CI: 1.05–1.43). Similarly, Chen et al. [131] conducted another cohort study on 284 patients and described that oseltamivir did not shorten viral RNA clearance, particularly in non-serious patients. Moreover, several clinical trials (for instance, NCT04303299, NCT04516915, NCT04338698, and so on) are ongoing to evaluate the effectiveness of oseltamivir in treating SARS-CoV-2 infection.

3.7. Darunavir (DRV)

Darunavir (DRV) is a second-generation protease inhibitor extensively used to treat HIV infection with cobicistat as a pharmacokinetic booster [138,139]. Several studies reported that DRV could inhibit COVID-19 enzymatic proteins by inhibiting the chymotrypsin-like protease of SARS-CoV-2 [139,140].

Deng et al. [65] evaluated the safety and efficacy of darunavir/cobicistat (DRV/c) in COVID-19-infected patients in Zhongnan Hospital of Wuhan University. They worked

on a total of 66 patients (DRV/c = 32 and control group = 34) and found that the nucleic acid conversion duration was significantly shorter in the DRV/c group from the onset of symptoms to admission within three days (7.9 ± 6.7 days) than above three days (15.9 ± 7.1 days) ($p = 0.01$). Meriglier et al. [108] conducted another study on 46 patients (HCQ + DRV/RTV = 25 and HCQ + LPV/RTV = 21) and found that the combination therapy of HCQ and DRV/RTV showed ECG abnormalities, mostly in older (age = 70) patients with hypertension, chronic cardiovascular disease, and kidney failure.

In another report, Kim et al. [66] observed 110 critically ill hospitalized SARS-CoV-2-infected patients (DRV-c group = 14 and control = 96) in Korea. After 1:2 propensity-score matched analysis, DRV-c group also showed a lower fatality rate than the controls (OR 0.07, 95% CI 0.01–0.52, $p = 0.009$). Chen et al. [67] conducted a randomized open-label trial (NCT04252274) on 30 patients (DRV/c = 15 and control = 15) with SARS-CoV-2-infected patients. The difference of negative PCR conversion rate in between two groups at day 7 was 13.3% (DRV/c vs. control = 9/15 (60.0%) vs. 7/15 (46.7%), respectively; $p = 0.72$). At day 3, viral clearance was 20% (3/15) in both groups and at day 5, the difference of negative PCR conversion rate between the two groups was 6.7% (DRV/c vs. control = 26.7% (4/15) vs. 20% (3/15), respectively).

4. Discussion and Concluding Remarks

The new emergence of such a deadly virus needs potential agents to control it. It can be noted that mass vaccination is not easily affordable in many developing and underdeveloped countries immediately or before 2024 [141]. Additionally, over-populated countries might face some critical situations to ensure vaccines for all people due to vaccine insufficiency, and it might take longer to eradicate the outbreak. Moreover, the delta variant of concern has shown to be several times more resistant against vaccine-induced immunity [142]. This crucial situation calls for effective treatment tools/antiviral agents to fight against the deadly infectious disease. This review mainly focuses on the efficiency and adverse effects of repurposing antiviral drugs potentially used to treat COVID-19.

Various drugs are being used as repurposing drugs, as there is no drug or effective treatment strategy against COVID-19. Therefore, the most promising seven antiviral drugs were taken under consideration to evaluate their efficacy and also their adverse effects in various levels of COVID-19 patients.

The very first drug and most widely used one was RDV. Though several studies mentioned above showed reduced mortality, shorter hospital stay, and better improvement of symptoms, several studies have been reported it to be insignificant in the case of COVID-19 patients' recovery. Notably, the Macaque experiment stated that RDV was only efficient in viral clearance from the lower respiratory tract, not the upper one [143]. Another randomized controlled study conducted by Wang et al. [37] suggested no efficacy of RDV on the respiratory tract, neither upper nor lower. We can conclude by evaluating the above data that RDV might be effective for severe patients in mitigating the fatality rate and improvement of clinical conditions. The WHO has recommended RDV against in non-severe patients, which might match with the current findings.

FPV has shown great efficacy in this crucial situation, yet it is not patient-friendly due to its high dose. The studies discussed above revealed that FPV is a potential cure for COVID-19, both in severe and mild cases. Chen et al. [44] reported a positive effect of FPV compared to ARB, as the former showed better improvement of symptoms like cough, pyrexia, and difficulty breathing. The drug is beneficial in alleviating symptoms, reducing viral load and hospital stay, but still, it is considered risky due to severe side effects like teratogenicity and embryotoxicity [144]. This drug was very effective against H1N1 virus, which is also an RNA virus and has shown potential antiviral effects, perhaps most efficient in viral clearance. There has been no toxicity detected for its huge loading dose, but some adverse effects have been reported; cardiovascular complications, nausea, vomiting, diarrhea, and kidney injuries are the common ones. Several studies also compared the efficacy among FPV, hydroxychloroquine, chloroquine, and IFN, which had minimal

significant difference. LPV/RTV combination was also a drug of choice for COVID-19 in the early stages of the pandemic. However, this combination proved to be insignificant in most of the cases studied, with some exceptions. The combination rather became the reason behind serious complications like diarrhea, gastrointestinal disturbance, electrolyte imbalance, and severe acute kidney injury in patients with both severe and mild COVID-19.

INF therapy is one of the promising treatments for COVID-19 now. Several subcategories of INF are known, such as IFN-alpha 1a, IFN-alpha 1b, IFN-beta 1a, IFN-beta 1b, IFN-gamma, and IFN-lambda. All have shown a variety of efficacy without severe side effects. They have worked to the betterment of patients' condition and reduced the fatality rate among severe patients. Several studies were also carried out to evaluate and compare the potentials of these variants. Recombinant IFN has proven to be more potent than traditional ones. An efficient therapy known as triple therapy is a combination of IFN/LPV/r/RBV that has shown amazing results. Type I interferons (IFN-I, IFN- α , and IFN- β) are immunomodulatory drugs that can induce antiviral effects and may induce pro-inflammatory activity, which has turned out to be beneficial for early treatment of COVID-19 [145]. Combination with other antiviral agents may mitigate the adverse effects as well as improve the clinical condition of the patients.

ARB has shown noteworthy effects in alleviating symptoms of COVID-19 and shortening the time for converting the PCR result from positive to negative. The potential antiviral agent works well both alone and in combination with various other agents like HCQ, RBV, and IFN. Antibiotic therapy alongside ARB is just the icing on the cake, showing prompt activity in quick recovery and reduction of fatality rate. It has proved to be more efficacious than other drugs like LPV/RTV and HCQ. All these have made it a potential agent in this pandemic situation. We can add oseltamivir to this list, but the drug showed great positive effects in severe patients when used early. Darunavir is emerging as a potent antiviral drug by lowering the mortality rate and hospital stay, but more studies are required to extensively verify its safety profile.

HCQ, LPV/RTV, and many other drugs, which were thought to be a treatment option earlier, are already banned by the WHO. FPV, ARB, and oseltamivir are in the pool of acceptable drugs for COVID-19, but there are still many randomized trials going on to assess their safety profiles. RDV is recommended in severe conditions considering its adverse effects that require limited use of the drug. Boosting the immune system is believed to be beneficial, so IFN type I might exert immunomodulation through its antiviral effects by stimulating interferon-stimulated gene (ISG).

As patients with COVID-19 might face multiple pathological dysfunctions, they must be prescribed multi-drug therapies [146]. Moreover, several pieces of evidence have demonstrated that combination therapy is superior to monotherapy, as the multiple drugs might heal by acting on multiple receptors [147]. Particularly, combination therapy in COVID-19 has become an excellent choice to wrestle against the disease. Several diagnoses revealed that secondary infections have become of paramount importance as an after-effect of COVID-19, and have some saddening consequences. A combination of potential antivirals with antibiotics is used to fight the secondary infections produced due to lessened immunity, along with the viral infection [148]. Interferon uses an immunomodulator that has served well for COVID-19, and its combination with antiviral agents gives the best results. Moreover, the combination lowers the time taken to reduce viral shedding significantly [149]. The mechanism could be the dual action of antivirals and immunomodulatory agents; one weakens the virus, and the latter strengthens the immunity so the body can recover faster, through confirmation or justification of this mechanism is yet to be provided. However, to define the exact mechanism and efficacy profile of the stated combinations in the current review, more precise investigation with larger data and evidence might be required.

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Abbreviations

RDV	remdesivir
FPV	favipiravir
LPV-RTV	lopinavir-ritonavir
INF	interferon
rhIFN- α	recombinant human interferon alpha
rSIFN	recombinant super compound interferon
TFF2	trefoil factor 2
ARB	arbidol
DRV	darunavir
DRV/c	darunavir/cobicisitat
HCQ	hydroxychloroquine
CQ	chloroquine
RCT	randomized controlled trial
LHQW	Lianhuaqingwen
LQ	Lianhua Qingwen
CP	convalescent plasma
BCN	baricitinib
RBV	ribavirin
SFV/DCV	sofosbuvir/daclatasvir
N	number
T	treatment (group)
C	control (group)
SOC	standard of care
CT	computed tomography
IV	intravenous
NA	not available
SC	subcutaneous
GI	gastrointestinal
95% CI	95% confidence interval
HR	hazard ratio
OR	odds ratio
RR	relative risk
ROA	route of administration
ADR	adverse drug reaction
ADRS	acute respiratory distress syndrome
ALT	alanine aminotransferase
RdRp	RNA-dependent RNA polymerase
IQR	interquartile range
PCR	polymerase chain reaction
ECG	electrocardiogram

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