Narrative Review of Anti-Retrovirals Used in COVID-19 Treatment

by Aditya Sindu Sakti

Submission date: 24-Oct-2024 10:05AM (UTC+0700)
Submission ID: 2495426505
File name: rip_Journal_of_Clinical_Pharmacy_and_Pharmaceutical_Science.docx (69.33K)
Word count: 6700
Character count: 40245

Narrative Review of Anti-Retrovirals Used in COVID-19 Treatment

Aditya Sindu Sakti*
Department of Pharmacognosy and Phytochemistry, Faculty of Health Sciences, Universitas Muhammadiyah Lamongan, Lamongan, Indonesia

Irma Susanti
Department of Clinical and Community Pharmacy, Faculty of Health Sciences, Universitas Muhammadiyah Lamongan, Lamongan, Indonesia

Djati Wulan Kusumo
Department of Pharmacognosy and Phytochemistry, Faculty of Health Sciences, Universitas Muhammadiyah Lamongan, Lamongan, Indonesia

Alamat: Jalan Plalangan Plosowahyu KM 03, Lamongan, Jawa Timur, Indonesia
Korespondensi penulis: adityasindu@umla.ac.id.com

Abstract. *The COVID-19 pandemic has necessitated the exploration of various therapeutic strategies, including the repurposing of existing antiviral drugs. This narrative review examines the use of anti-retroviral agents in the treatment of COVID-19, focusing on their mechanisms of action, efficacy, and safety profiles. Key antiretrovirals discussed include Remdesivir, Lopinavir/Ritonavir, Ribavirin, Oseltamivir, Favipiravir, and Sofosbuvir. These agents primarily act by inhibiting RNA-dependent RNA polymerase (RdRp), a critical enzyme in the replication cycle of SARS-CoV-2. Clinical trials and in vitro studies have provided mixed results regarding their effectiveness, with some agents showing promise in reducing mortality and improving recovery times, while others have demonstrated limited efficacy. The review highlights the urgent need for further clinical research to optimize antiviral regimens and improve patient outcomes in the ongoing battle against COVID-19.*

Keywords: *COVID-19, anti-retroviral, SARS-CoV-2; RNA-dependent RNA polymerase; antiviral therapy.*

Abstrak. Pandemi COVID-19 telah mendorong eksplorasi berbagai strategi terapeutik, termasuk penggunaan kembali obat antivirus yang sudah ada. Tinjauan naratif ini mengkaji penggunaan agen anti-retroviral dalam pengobatan COVID-19, dengan fokus pada mekanisme kerja, efektivitas, dan profil keamanannya. Beberapa anti-retroviral utama yang dibahas meliputi Remdesivir, Lopinavir/Ritonavir, Ribavirin, Oseltamivir, Favipiravir, dan Sofosbuvir. Agen-agen ini terutama bekerja dengan menghambat RNA-dependent RNA polymerase (RdRp), enzim krusial dalam siklus replikasi SARS-CoV-2. Uji klinis dan studi in vitro telah memberikan hasil yang beragam mengenai efektivitasnya, dengan beberapa agen menunjukkan potensi dalam mengurangi angka kematian dan mempercepat pemulihan, sementara yang lain menunjukkan efektivitas terbatas. Tinjauan ini menekankan perlunya penelitian klinis lebih lanjut untuk mengoptimalkan rejimen antiviral dan meningkatkan hasil pengobatan pasien dalam menghadapi COVID-19.

Kata kunci: COVID-19, anti-retroviral, SARS-CoV-2, RNA-dependent RNA polymerase, terapi antivirus.

INTRODUCTION

The COVID-19 pandemic, which emerged in 2019, remains a significant global health crisis. By the end of 2020, the World Health Organization had documented over 54 million confirmed cases worldwide, with more than 1.3 million fatalities (WHO, 2020). Indonesia has been notably affected, with a death toll of 16,945 out of 538,883 confirmed cases as of November 2020 (Kemenkes RI, 2020). In addition to preventive measures, enhancing therapeutic interventions is crucial to reduce the mortality rate among COVID-19 patients. Although vaccine development is ongoing, the immediate need posed by the pandemic has led to the repurposing of existing drugs as potential treatment options. Various therapeutic strategies have been implemented, particularly for patients in severe condition (Sadeghi et al., 2020; Setiadi et al., 2020).

Coronaviruses are large, enveloped, single-stranded RNA viruses capable of infecting a diverse range of species, including humans and various mammals like dogs, cats, cattle, and pigs (Channappanavar et al., 2014; Wiersinga et al., 2020). These viruses are divided into four genera—α, β, γ, and δ—based on their genetic characteristics. The α and β coronaviruses primarily infect mammals (Rabi et al., 2020). SARS-CoV-2, which causes COVID-19, belongs to the Coronaviridae family (Wu & McGoogan, 2020). Human coronaviruses such as 229E and NL63, which lead to common respiratory illnesses like colds and croup, are classified within the α genus, whereas SARS-CoV, MERS-CoV, and SARS-CoV-2 are part of the β genus (Yuki et al., 2020).

The primary mode of SARS-CoV-2 transmission is through respiratory droplets from coughs or sneezes. Once inhaled, the virus targets type 2 alveolar epithelial cells (AT2) in the lungs, which are responsible for producing surfactant to reduce alveolar surface tension and prevent collapse. SARS-CoV-2 spike proteins have been found to bind with ACE-2 receptors on these cells (Li et al., 2019; Wang et al., 2020). ACE2 has been identified as the key receptor for SARS-CoV, with high expression levels observed in the lungs, heart, ileum, kidneys, and bladder (Zou et al., 2020). The roles of ACE2 and TMPRSS2, a cellular serine protease, are critical in facilitating the entry of SARS-CoV-2 into host cells, integrins may cause conformational changes in ACE2 when interacting with the virus (Hoffmann et al., 2020). Like other respiratory viruses such as influenza, SARS-CoV-2 can result in severe lymphopenia by targeting and destroying T lymphocytes. The virus-induced inflammatory response, involving both innate and

adaptive immunity, hinders lymphopoiesis and increases lymphocyte apoptosis (Vaduganathan et al., 2020). As the infection progresses and viral replication accelerates, the integrity of the epithelial-endothelial barrier deteriorates. SARS-CoV-2 additionally targets pulmonary capillary endothelial cells, intensifying the inflammatory response and leading to the infiltration of monocytes and neutrophils. Autopsy reports have shown widespread thickening of alveolar walls, with mononuclear cells and macrophages invading air spaces, resulting in endotheliitis (Xu et al., 2020). Once inside the host cells, the virus releases its positive-sense single-stranded RNA (ssRNA), which hijacks the host's ribosomes to produce polyproteins and RNA-dependent RNA polymerase, both crucial for RNA replication. The spike proteins produced are distributed by cellular packaging structures to vesicular carriers, while cytoplasmic proteases break down the synthesized polyproteins into their components, such as nucleocapsid enzymes, spike protein, M-protein, and E-protein (Sigrist et al., 2020).

SARS-CoV-2 has the ability to induce the release of pro-inflammatory cytokines, such as interleukin (IL)-6, IL-10, tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein 1 (MCP1), granulocyte-colony stimulating factor (G-CSF), and macrophage inflammatory protein (MIP) 1α (Gong et al., 2020; Qin et al., 2020; Zhou et al., 2020). These cytokines cause vasodilation and increase vascular capillary permeability, leading to plasma leakage into the alveolar interstitial space, which accumulates and exerts pressure on the alveoli (Wu et al., 2020). Elevated IL-6 levels have been associated with worse prognoses and greater clinical severity in COVID-19 patients (Ulhaq & Soraya, 2020). Moreover, COVID-19 patients have shown a greater proportion of specific inflammatory receptors, such as CD14 and CD16 monocytes, are observed, which contribute to IL-6 production and trigger a systemic inflammatory response. The overproduction and release of pro-inflammatory cytokines play a key role in the "cytokine storm," which can overpower the immune system and result in acute respiratory distress syndrome (ARDS) and multi-organ dysfunction syndrome (MODS) (Nile et al., 2020).

The primary therapeutic strategy for COVID-19 focuses on symptomatic and supportive care. During the acute phase, immune-boosting drugs may be administered, while immunosuppressants can be considered in advanced or critical stages. Potential therapeutic options include chloroquine, hydroxychloroquine, antibiotics, tocilizumab, COVID-19 convalescent plasma, corticosteroids, vitamin B3, extracorporeal membrane

oxygenation (EMCO), and antivirals. Nonetheless, no specific treatment has been conclusively demonstrated to be effective against COVID-19 (Sugitha, 2020). The choice of therapy should be individualized, weighing the benefits and risks of each drug. Numerous studies have been conducted to identify effective treatments, including the evaluation of antiviral effectiveness in COVID-19 therapy. This review will summarize the use of various antiviral drugs as potential therapeutic options for COVID-19.

METHODOLOGY

Scientific and clinical data related to the use of potential antiretroviral agents for the treatment of SARS-CoV-2 were collected through a comprehensive literature search. This search was conducted using the Google Scholar search engine with the keyword "SARS-CoV-2".

RESULTS AND DISCUSSION

In this review, we compiled data on five antiretroviral agents that have been utilized in clinical settings to potentially treat SARS-CoV-2, aiming to reduce the mortality associated with COVID-19. The antiretrovirals examined include Remdesivir, Lopinavir/Ritonavir, Ribavirin, Oseltamivir, Favipiravir, and Sofosbuvir. These drugs primarily function as inhibitors of RNA-dependent RNA polymerase (RdRp), a key enzyme in the replication cycle of RNA viruses. Focusing on RdRp has been a widely used approach in treating several viral infections, including hepatitis C virus (HCV), Zika virus (ZIKV), and human coronaviruses (HCoVs) (Elfiky, 2020). SARS-CoV-2, the virus responsible for COVID-19, shares about 79% of its genetic structure with SARS-CoV and approximately 50% with MERS-CoV (Gupta et al., 2020). The RdRp enzymes of SARS-CoV, SARS-CoV-2, and MERS-CoV are closely related (Wang et al., 2020), making RdRp a broad-spectrum target for identifying effective COVID-19 treatments. The antiretroviral agents listed in Table I are recognized by RdRp as substrates, thereby disrupting the replication of SARS-CoV-2 (Wang et al., 2020). In vitro studies have indicated that Remdesivir stands out as the most effective RdRp inhibitor, with an EC_{50} value of 0.77 μM, which is significantly lower compared to Lopinavir/Ritonavir (EC_{50} = 26.1 μM), Ribavirin (EC_{50} = 109.5 μM), and Favipiravir (EC_{50} = 61.88 μM).

Lopinavir/Ritonavir and Oseltamivir operate through different mechanisms. Lopinavir/Ritonavir acts as a protease inhibitor, while Oseltamivir inhibits neuraminidase via competitive inhibition. Protease inhibition has also been explored as a strategy for

developing effective antiretroviral therapies against SARS-CoV-2. Proteases are enzymes that cleave proteins, a process essential for viral protein maturation. The primary protease responsible for cleaving polyproteins into functional proteins in SARS-CoV-2 is the 3 Chymotrypsin-like protease (3CL) (Li & Kang, 2020). Lopinavir/Ritonavir has demonstrated the ability to inhibit 3CL in vitro, with an EC_{50} value of 50 μM and a Ki of 14 μM (Wu et al., 2004). However, some studies have questioned the clinical effectiveness of Lopinavir/Ritonavir as a protease inhibitor, noting that in vitro EC_{50} data does not always translate into significant clinical improvements (Baden & Rubin, 2020; Cao et al., 2020; Horby et al., 2020). Oseltamivir, originally developed for treating influenza A and B, inhibits neuraminidase activity. Despite its early use during the COVID-19 outbreak, it was later discovered that SARS-CoV-2 does not express neuraminidase (Tan et al., 2020).

Sofosbuvir, which was previously used to treat SARS-CoV, has not been shown to inhibit SARS-CoV-2 according to bioinformatics studies (Jácome et al., 2020). Clinically, Sofosbuvir has been approved for treating hepatitis C virus (HCV) infection. Given the similarities in replication patterns between SARS-CoV-2 and HCV, there is a hypothesis that Sofosbuvir could be repurposed for treating SARS-CoV-2 (Sayad et al., 2020). To enhance clinical efficacy and prevent drug resistance, Sofosbuvir is currently administered in combination with other antiretroviral agents (Jockusch et al., 2020).

Table 1. Mechanism of Action, Dosage, Pharmacokinetic Profile, and Side Effects of Selected Antiretrovirals Potentially Used for COVID-19 Treatment

Antiviral Agent	Mechanism of Action	Dosage	Pharmacokinetic Profile and Side Effects
Remdesivir	Remdesivir, a nucleotide analog, is recognized by RNA-dependent RNA polymerase (RdRp) as a substrate. The complex formed between RDV and RdRp interferes with the termination process, effectively inhibiting the replication of MERS-CoV, SARS-CoV, and SARS-CoV-2, with an EC_{50} value of 0.77 μM (Gordon et al., 2020; M. Wang et al., 2020).	Intravenous loading dose of 200 mg/24 hours, followed by a maintenance dose of 100 mg/24 hours for 5 to 9 days (Sun, 2020).	Metabolized by cytochrome P450 enzymes CYP2C8, CYP2D6, and CYP3A4. Elimination half-life (t½) = 0.89 hours. AUC24 (Area Under Curve) over 24 hours of intravenous administration = 3,478.5 ng×h/ml, SEM = 923.5 ng×h/ml. Peak serum concentration (Cmax) = 2,737 ± 1,985 ng/ml and 4,042 ng/ml (Gordon et al., 2020). Side effects: Elevated liver enzymes, constipation, nausea, respiratory failure (Fan et al., 2020).

Lopinavir/Ritonavir	Lopinavir functions as a competitive inhibitor of protease, and at a concentration of 50 μM, it disrupts SARS-CoV chymotrypsin-like (3CL) protease, thereby interfering with proteolysis and leading to the formation of immature viral particles (Uzunova et al., 2020; Wu et al., 2004). It also hinders the replication of MERS-CoV and SARS-CoV, with an EC_{50} of 8.0 μM (Goldman et al., 2020). In Vero E6 cells infected with SARS-CoV-2, lopinavir shows an inhibitory effect on replication, with an EC_{50} of 26.1 μM (Choy et al., 2020). Ritonavir, when used in low doses, enhances the pharmacokinetics of lopinavir by inhibiting cytochrome P450 CYP3A4, thereby acting as a booster (Meini et al., 2020).	The suggested dosage for treating SARS-CoV-2 is 200/50 mg to 400/100 mg administered every 12 hours for a duration of 7 to 10 days (Kim et al., 2020; Meini et al., 2020).	Lopinavir/Ritonavir is primarily metabolized by cytochrome P450 CYP3A4 (F. Li et al., 2012). Elimination half-life (t½) = 4.0 hours. AUC12 after 10 days of oral administration = 102.9 ± 26.09 mg×h/L. Peak serum concentration (Cmax) = 12.3 ± 3.22 mg/L (la Porte et al., 2004). Side effects: Diarrhea, nausea, vomiting, hyperlipidemia, glucose intolerance (Chandawi & Shuter, 2008).
Ribavirin	Prevents viral RNA synthesis and mRNA capping (Falzarano et al., 2013); attaches to SARS-CoV-2 RdRp, thereby hindering replication. In vitro studies on Vero E6 cells demonstrate an EC_{50} of 109.5 μM (Wang et al., 2020).	500 mg/12 hours intravenously (Tong et al., 2020); 600 mg/12 hours for 9 days (Eslami et al., 2020).	Elimination half-life (t½) = 37.0 ± 14.2 hours. AUC12 for oral administration = 37.2 mg×h/L. Peak serum concentration (Cmax) = 4,187 ng/ml and 638 ng/ml for intravenous and oral administration, respectively (G. F. Hoffmann & McKiernan, 2017; Rower et al., 2015). Side effects: Anemia, gastrointestinal disturbances, nausea, vomiting (Eslami et al., 2020).
Oseltamivir	Competitively inhibits neuraminidase, preventing viral release from cells and hindering virus crossing the respiratory mucosal layer (Hu et al., 2020).	300 mg/day (Tan et al., 2020).	Oseltamivir is a prodrug that is converted into its active form, oseltamivir carboxylate, through hydrolysis. Bioavailability is 75%, peak plasma concentration at 2.5-6 hours, protein binding: 3% (oseltamivir carboxylate), 42% (oseltamivir). Elimination half-life (t½) = 1-3 hours (oseltamivir), 6-10 hours (oseltamivir carboxylate), excreted in feces; > 90% in urine as oseltamivir carboxylate (Chien et al., 2020). Side effects: Abdominal pain, conjunctivitis, ear disorders, epistaxis, insomnia, nausea, vomiting, vertigo (Tan et al., 2020).
Sofosbuvir	Suppresses the RNA-dependent RNA	400 mg/day (Eslami et al., 2020).	Peak plasma concentration: 0.2-2 hours, protein binding: 61-65%,

	polymerase (RdRp) activity of SARS-CoV (Chien et al., 2020).		excreted in urine (78% as GS 331007 metabolite, 3.5% as sofosbuvir), t½ = 0.4 hours (Eslami et al., 2020).
Favipiravir	Blocks RNA polymerase activity, with an EC_{50} of 61.88 μM (Wang et al., 2020).	800-1800 mg/12 hours, maximum duration up to 14 days.	Bioavailability: 94%, protein binding: 54%, Cmax at 2 hours after a single dose, tmax and t½ increase with multiple doses, t½ = 2.5-5 hours, rapidly eliminated by the kidneys in a hydroxylated form (Agrawal et al., 2020).

This review evaluated the effectiveness of various antiviral combinations for treating COVID-19. The regimen that included interferon beta-1b, Lopinavir/Ritonavir, and Ribavirin significantly shortened the time from the initiation of treatment to a negative nasopharyngeal swab result (7 days) compared to the control group (12 days). This treatment regimen also shortened both the duration of viral shedding and the length of hospital stay for patients with mild to moderate COVID-19. Side effects like nausea and diarrhea were generally mild and showed no significant differences between the two groups. It is noteworthy that one patient in the control group discontinued antiretroviral therapy due to hepatitis; however, no deaths were reported during the study (Hung et al., 2020).

The duration required for viral clearance varied across different antiviral combinations: Lopinavir/Ritonavir and IFN-α took 12 days, Ribavirin and IFN-α took 13 days, and Ribavirin with Lopinavir/Ritonavir took 15 days. The highest percentage of SARS-CoV-2 negative patients was observed in the Lopinavir/Ritonavir and IFN-α group (61.1%), followed by the Ribavirin and IFN-α group (51.5%), and the Ribavirin, Lopinavir/Ritonavir, and IFN-α group (46.9%) after 14 days of observation. However, these differences were not statistically significant. Gastrointestinal side effects were more common in the Ribavirin, Lopinavir/Ritonavir, and IFN-α group compared to the other groups (Huang et al., 2020).

Sofosbuvir combined with Daclatasvir and Hydroxychloroquine reduced hospital stay duration in COVID-19 patients (6 days) compared to Hydroxychloroquine combined with Lopinavir/Ritonavir (8 days). The intervention group was administered Sofosbuvir and Daclatasvir (400/60 mg once daily) with or without Lopinavir/Ritonavir (200/50 mg twice daily), whereas the control group was given only Lopinavir/Ritonavir (200/50 mg twice daily). Additionally, both groups were treated with Hydroxychloroquine (200 mg twice daily) (Sadeghi et al., 2020).

The combination of Sofosbuvir, Daclatasvir, and Ribavirin did not reduce the length of hospital stay; however, the cumulative recovery rate was higher, with fewer patients requiring ICU admission compared to the control group. The intervention group was treated with Sofosbuvir and Daclatasvir (400/60 mg once daily) in combination with Ribavirin (600 mg twice daily), whereas the control group was administered Hydroxychloroquine (400 mg as a single dose) and Lopinavir/Ritonavir (400/100 mg twice daily) with or without Ribavirin (600 mg twice daily). A limitation of this study was the small sample size and the higher median age in the control group compared to the intervention group (Kasgari et al., 2020).

In a study comparing Remdesivir to a placebo, no significant difference was found in clinical improvement; however, patients treated with Remdesivir showed faster clinical recovery (less than 10 days). Adverse effects were reported in 66% of the intervention group and 64% of the placebo group (Wang et al., 2020). There was no statistically significant difference in clinical status between patients treated with Remdesivir for 10 days and those who received standard care. However, those who received a 5-day course of Remdesivir showed statistically significant clinical improvement compared to the standard care group. The average treatment duration was 5 days for the 5-day Remdesivir group and 6 days for the 10-day group. By day 11, patients in the 5-day Remdesivir group experienced statistically significant clinical improvement compared to those in the standard care group, whereas no significant difference was observed between the 10-day Remdesivir group and the standard care group. By day 28, nine patients had died: two (1%) from the 5-day Remdesivir group, three (2%) from the 10-day Remdesivir group, and four (2%) from the standard care group. Side effects, including nausea, hypokalemia, and headaches, were more commonly reported in patients treated with Remdesivir than in those receiving standard care (Spinner et al., 2020).

Tabel 2. Mechanism of Action, Dosage, Pharmacokinetic Profile, and Side Effects of Selected Antiretrovirals Potentially Used for COVID-19 Treatment

Trial ID and Reference	Location	Design	Number of Patients	Intervention	Control	Inclusion Criteria	Primary Outcome
NCT04276688 (Hung et al., 2020)	Hong Kong, China	Open-label randomized controlled trial	127	The combination treatment included Lopinavir/ritonavir at 400	Lopinavir/ritonavir 400 mg/100 mg twice daily (n=41)	1. Adults aged 18 years or older 2. Body temperature of 38°C or	The duration until a negative SARS-CoV-2 result is obtained in

				mg/100 mg taken twice daily, Ribavirin at 400 mg taken twice daily for 14 days, and Interferon Beta-1B administered subcutaneously at 0.25 mg for 3 days (n=86).		higher accompanied by symptoms such as cough, sputum production, sore throat, nasal discharge, myalgia, headache, or fatigue 3. Symptoms present for 10 days or less	nasopharyngeal swab samples.
IRCT20200324046850N2 (Eslami et al., 2020)	Tehran, Iran	Open-label trial	62	Combination of Sofosbuvir/Daclatasvir 400/60 mg	Ribavirin 600 mg every 12 hours	1. Positive RT-PCR nasopharyngeal swab result 2. O_2 saturation <94%	Time from treatment initiation to hospital discharge
ChiCTR2000029387 (Huang et al., 2020)	China	Open-label randomized controlled trial	101	Combination of Ribavirin 2 g intravenously (loading dose) followed by 400-600 mg every 8 hours + IFN-α 50 mg twice daily (n=33)	Combination of Lopinavir/ritonavir + IFN-α 50 mg twice daily (n=36); Combination of Lopinavir/ritonavir + IFN-α 50 mg twice daily + Ribavirin 2 g intravenously (loading dose) followed by 400-600 mg every 8 hours (n=32)	1. Aged 18-65 years 2. Confirmed diagnosis of mild to moderate COVID-19	Time from antiviral treatment initiation to negative SARS-CoV-2
IRCT20200328046886N1 (Abbaspour Kasgari et al., 2020)	Mazandaran, Iran	Randomized clinical trial	48	Combination of Sofosbuvir/Daclatasvir 400/60 mg + Ribavirin 600 mg twice daily	Hydroxychloroquine (400 mg as a single dose) and Lopinavir/ritonavir (400/100 mg taken twice daily), with or without Ribavirin (600 mg administered twice daily).	1. Aged 18-80 years 2. Confirmed diagnosis of mild to moderate COVID-19 3. Respiratory rate <24/min 4. O2 saturation <94%	Length of hospital stay
NCT04257656 (Wang et al., 2020)	Wuhan, China	Randomized, double-blind, placebo-controlled, multicenter trial	237	Remdesivir was administered intravenously at a dose of 200 mg on the first day, followed by a daily infusion of 100 mg from day 2 to day 10 (n=158).	Placebo administered with the same volume (n=79)	1. Not pregnant 2. Aged ≥18 years 3. Pneumonia present 4. O_2 saturation <94% 5. PaO_2 <300 mmHg	Clinical improvement after 28 days

NCT04292730 (Spinner et al., 2020)	USA, Europe, Asia	Randomized controlled trial	596	Remdesivir was given intravenously at a dose of 200 mg on the first day, followed by 100 mg on the following days as part of 5-day and 10-day regimens (n=396).	Standard care (n=200)	1. Positive COVID-19 pneumonia 2. O_2 saturation >94%	Distribution of clinical status using a 7-point ordinal scale on day 11 of the study.
ChiCTR2000030254 (Chen et al., 2020)	Wuhan, China	Open-label, prospective, randomized (multicenter)	236	Favipiravir administered at 1600 mg twice daily on day 1, followed by 600 mg twice daily from days 2 to 10, in addition to standard care (n=116).	Arbidol (Umifenovir) at 200 mg taken three times daily, in addition to standard care (n=120).	1. Positive COVID-19 pneumonia 2. Symptom onset within 12 days	Clinical improvement rate at 7 days
ChiCTR2000029600 (Cai et al., 2020)	Shenzhen, China	Open-label, non-randomized	80	Favipiravir at a dosage of 1600 mg twice daily on the first day, followed by 600 mg twice daily from days 2 to 14, combined with inhaled aerosol IFN-α 5 iu administered twice daily (n=35).	Lopinavir at 400 mg combined with Ritonavir at 100 mg, both administered twice daily, along with inhaled aerosol IFN-α at 5 iu twice daily (n=45).	1. Positive COVID-19 by swab 2. Aged 16-75 years 3. Symptom onset ≤7 days	Viral clearance
IRCT20200128046294N2 (Sadeghi et al., 2020)	Tehran, Iran	Open-label randomized (multicenter)	66	Sofosbuvir and Daclatasvir at 400/60 mg taken once daily, combined with Hydroxychloroquine at 200 mg twice daily, with or without Lopinavir/Ritonavir at 200/50 mg twice daily (n=33).	Lopinavir/Ritonavir at 200/50 mg administered twice daily, combined with Hydroxychloroquine at 200 mg twice daily (n=33).	1. Positive COVID-19 by swab/chest CT Hospitalized 2. Oral temperature ≥37.8°C, O_2 saturation <94%, RR >24/min 3. Symptom onset ≤8 days	Recovery within 14 days

The comparison between Favipiravir and Arbidol showed no significant difference in clinical improvement on day 7, although mild and manageable side effects were associated with Favipiravir use. The intervention group received Favipiravir (1600 mg twice daily on the first day, followed by 600 mg twice daily from day 2 to day 10), while the control group received Arbidol (200 mg three times daily) alongside standard therapy (which included traditional Chinese medicine, additional antivirals, antibiotics, immunomodulators, psychotropics, nutritional supplements, cardiovascular drugs, and invasive/non-invasive ventilation) for 7 days (Chen et al., 2020).

Favipiravir showed superior results in terms of disease progression and viral clearance when compared to the control group. The intervention group was administered Favipiravir (1600 mg twice daily on the first day, followed by 600 mg twice daily from day 2 to day 14), while the control group was given Lopinavir/Ritonavir (400 mg/100 mg twice daily). Additionally, both groups received aerosolized IFN-α inhalation therapy (5 iu twice daily) (Cai et al., 2020).

CONCLUSION

The use of anti-retroviral agents in the treatment of COVID-19 has been explored with varying degrees of success. This review highlights that while some agents such as Remdesivir have shown promise in reducing viral load and improving clinical outcomes, others, like Lopinavir/Ritonavir, have demonstrated limited efficacy. The inhibition of RNA-dependent RNA polymerase (RdRp) remains a crucial mechanism for targeting SARS-CoV-2. However, the mixed results across clinical trials underline the necessity for continued research to optimize antiviral regimens and improve therapeutic outcomes for COVID-19 patients. Future studies should focus on large-scale clinical trials to establish the most effective combinations of these agents, tailored to different stages of the disease and patient conditions.

ACKNOWLEDGEMENT

The authors would like to express their gratitude to the Lembaga Penelitian dan Pengabdian Kepada Masyarakat (LPPM) Universitas Muhammadiyah Lamongan for the internal grant provided, which greatly supported the completion of this research. We also extend our thanks to the Pusat Sentra HKI dan Publikasi Ilmiah Universitas Muhammadiyah for their financial support in covering the publication costs of this manuscript.

REFERENCES

Abbaspour Kasgari, H., Moradi, S., Shabani, A. M., Babamahmoodi, F., Davoudi Badabi, A. R., Davoudi, L., Alikhani, A., Hedayatizadeh Omran, A., Saeedi, M., Merat, S., Wentzel, H., Garratt, A., Levi, J., Simmons, B., Hill, A., & Tirgar Fakheri, H. (2020). Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: A single-centre, randomized controlled trial. *Journal of Antimicrobial Chemotherapy, 75* (11), 3373–3378. https://doi.org/10.1093/jac/dkaa332

Agrawal, U., Raju, R., & Udwadia, Z. F. (2020). Favipiravir: A new and emerging

antiviral option in COVID-19. *Medical Journal Armed Forces India, 76* (4), 370–376. https://doi.org/10.1016/j.mjafi.2020.08.004

Anand, K., Karade, S., Sen, S., & Gupta, R. (2020). SARS-CoV-2: Camazotz's Curse. *Medical Journal Armed Forces India, 76* (2), 136-141.

Baden, L. R., & Rubin, E. J. (2020). Covid-19 — The search for effective therapy. *New England Journal of Medicine, 382* (19), 1851–1852. https://doi.org/10.1056/NEJMe2005477

Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., Liao, X., Gu, Y., Cai, Q., Yang, Y., Shen, C., Li, X., Peng, L., Huang, D., Zhang, J., Zhang, S., Wang, F., Liu, J., Chen, L., ... Liu, L. (2020). Experimental treatment with favipiravir for COVID-19: An open-label control study. *Engineering, 6* (10), 1192–1198. https://doi.org/10.1016/j.eng.2020.03.007

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., Wei, M., Li, X., Xia, J., Chen, N., Xiang, J., Yu, T., Bai, T., Xie, X., Zhang, L., Li, C., ... Wang, C. (2020). A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine, 382* (19), 1787–1799. https://doi.org/10.1056/NEJMoa2001282

Chandawi, A., & Shuter, J. (2008). Lopinavir/ritonavir in the treatment of HIV-1 infection: A review. *Therapeutics and Clinical Risk Management, 4* (5), 1023–1033.

Channappanavar, R., Zhao, J., & Perlman, S. (2014). T cell-mediated immune response to respiratory coronaviruses. *Immunologic Research, 59n*(1–3), 118–128. https://doi.org/10.1007/s12026-014-8534-z

Chen, C., Zhang, Y., Huang, J., Yin, P., Cheng, Z., Wu, J., Chen, S., Zhang, Y., Chen, B., Lu, M., Luo, Y., Ju, L., Zhang, J., & Wang, X. (2020). Favipiravir versus Arbidol for COVID-19: A randomized clinical trial. *medRxiv*. https://doi.org/10.1101/2020.03.17.20037432

Chien, M., Anderson, T. K., Jockusch, S., Tao, C., Li, X., Kumar, S., Russo, J. J., Kirchdoerfer, R. N., & Ju, J. (2020). Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase, a key drug target for COVID-19. *Journal of Proteome Research, 19* (11), 4690–4697. https://doi.org/10.1021/acs.jproteome.0c00392

Choy, K.-T., Wong, A. Y.-L., Kaewpreedee, P., Sia, S. F., Chen, D., Hui, K. P. Y., Chu, D. K. W., Chan, M. C. W., Cheung, P. P.-H., Huang, X., Peiris, M., & Yen, H.-L. (2020). Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Research, 178,* 104786. https://doi.org/10.1016/j.antiviral.2020.104786

Elfiky, A. A. (2020). Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. *Life Sciences, 248,**117477. https://doi.org/10.1016/j.lfs.2020.117477

Elfiky, A. A. (2020). SARS-CoV-2 RNA dependent RNA polymerase (RdRp) targeting: An in silico perspective. *Journal of Biomolecular Structure and Dynamics,* 1–9. https://doi.org/10.1080/07391102.2020.1761882

Eslami, G., Mousaviasl, S., Radmanesh, E., Jelvay, S., Bitaraf, S., Simmons, B., Wentzel, H., Hill, A., Sadeghi, A., Freeman, J., Salmanzadeh, S., Esmaeilian, H., Mobarak, M., Tabibi, R., Jafari Kashi, A. H., Lotfi, Z., Talebzadeh, S. M., Wickramatillake, A., Momtazan, M., ... Mobarak, S. (2020). The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19. *Journal of Antimicrobial Chemotherapy, 75* (11), 3366–3372. https://doi.org/10.1093/jac/dkaa331

Falzarano, D., de Wit, E., Martellaro, C., Callison, J., Munster, V. J., & Feldmann, H. (2013). Inhibition of novel β coronavirus replication by a combination of interferon-

α2b and ribavirin. *Scientific Reports, 3,* 1686. https://doi.org/10.1038/srep01686

Fan, Q., Zhang, B., Ma, J., & Zhang, S. (2020). Safety profile of the antiviral drug remdesivir: An update. *Biomedicine & Pharmacotherapy, 130,* 110532. https://doi.org/10.1016/j.biopha.2020.110532

Glass, C. A., Cash, J. C., & Mullen, J. (2020). Coronavirus disease (COVID-19). In *Family Practice Guidelines*. Springer Publishing Company. https://doi.org/10.1891/9780826153425.0016b

Goldman, J. D., Lye, D. C. B., Hui, D. S., Marks, K. M., Bruno, R., Montejano, R., Spinner, C. D., Galli, M., Ahn, M.-Y., Nahass, R. G., Chen, Y.-S., SenGupta, D., Hyland, R. H., Osinusi, A. O., Cao, H., Blair, C., Wei, X., Gaggar, A., Brainard, D. M., & Subramanian, A. (2020). Remdesivir for 5 or 10 days in patients with severe COVID-19. *New England Journal of Medicine, 383* (19), 1827–1837. https://doi.org/10.1056/NEJMoa2015301

Gong, J., Dong, H., Xia, S. Q., Huang, Y. Z., Wang, D., Zhao, Y., Liu, W., Tu, S., Zhang, M., Wang, Q., & Lu, F. (2020). Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. *medRxiv*. https://doi.org/10.1101/2020.02.25.20025643

Gordon, C. J., Tchesnokov, E. P., Woolner, E., Perry, J. K., Feng, J. Y., Porter, D. P., & Götte, M. (2020). Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *Journal of Biological Chemistry, 295* (20), 6785–6797. https://doi.org/10.1074/jbc.RA120.013679

Hoffmann, G. F., & McKiernan, P. (2017). The single dose pharmacokinetics of ribavirin in subjects with chronic liver disease. In *Inherited Metabolic Diseases: A Clinical Approach* (pp. 203–226). https://doi.org/10.1007/978-3-662-49410-3_24

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N.-H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell, 181* (2), 271-280.e8. https://doi.org/10.1016/j.cell.2020.02.052

Horby, P. W., Mafham, M., Bell, J. L., Linsell, L., Staplin, N., Emberson, J., Palfreeman, A., Raw, J., Elmahi, E., Prudon, B., Green, C., Carley, S., Chadwick, D., Davies, M., Wise, M. P., Baillie, J. K., Chappell, L. C., Faust, S. N., Jaki, T., & Landray, M. J. (2020). Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (Recovery): A randomised, controlled, open-label, platform trial. *The Lancet, 396* (10259), 1345–1352. https://doi.org/10.1016/S0140-6736(20)32013-4

Hu, F., Yin, G., Chen, Y., Song, J., Ye, M., Liu, J., Chen, C., Song, Y., Tang, X., & Zhang, Y. (2020). Corticosteroid, oseltamivir and delayed admission are independent risk factors for prolonged viral shedding in patients with coronavirus disease 2019. *The Clinical Respiratory Journal, 14* (11), 1067–1075. https://doi.org/10.1111/crj.13243

Huang, Y. Q., Tang, S. Q., Xu, X. L., Zeng, Y. M., He, X. Q., Li, Y., Harypursat, V., Lu, Y. Q., Wan, Y., Zhang, L., Sun, Q. Z., Sun, N. N., Wang, G. X., Yang, Z. P., & Chen, Y. K. (2020). No statistically apparent difference in antiviral effectiveness observed among ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha, and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate coronavirus infection (COVID-19). *Frontiers in Pharmacology*. https://doi.org/10.3389/fphar.2020.01071

Hung, I. F. N., Lung, K. C., Tso, E. Y. K., Liu, R., Chung, T. W. H., Chu, M. Y., Ng, Y.

Y., Lo, J., Chan, J., Tam, A. R., Shum, H. P., Chan, V., Wu, A. K. L., Sin, K. M., Leung, W. S., Law, W. L., Lung, D. C., Sin, S., Yeung, P., & Yuen, K. Y. (2020). Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: An open-label, randomised, phase 2 trial. *The Lancet*.*https://doi.org/10.1016/S0140-6736(20)31042-4

Jácome, R., Campillo-Balderas, J. A., Ponce de León, S., Becerra, A., & Lazcano, A. (2020). Sofosbuvir as a potential alternative to treat the SARS-CoV-2 epidemic. *Scientific Reports, 10* (1), 9294. https://doi.org/10.1038/s41598-020-66440-9

Jockusch, S., Tao, C., Li, X., Chien, M., Kumar, S., Morozova, I., Kalachikov, S., Russo, J. J., & Ju, J. (2020). Sofosbuvir terminated RNA is more resistant to SARS-CoV-2 proofreader than RNA terminated by remdesivir. *Scientific Reports, 10* (1), 16577. https://doi.org/10.1038/s41598-020-73641-9

Kementerian Kesehatan Republik Indonesia. (2020). *Situasi COVID-19*. https://www.kemkes.go.id

Kim, S. B., Huh, K., Heo, J. Y., Joo, E.-J., Kim, Y. J., Choi, W. S., Kim, Y.-J., Seo, Y. Bin, Yoon, Y. K., Ku, N. S., Jeong, S. J., Kim, S.-H., Peck, K. R., & Yeom, J. S. (2020). Interim guidelines on antiviral therapy for COVID-19. *Infection & Chemotherapy, 52* (2), 281. https://doi.org/10.3947/ic.2020.52.2.281

la Porte, C. J. L., Colbers, E. P. H., Bertz, R., Voncken, D. S., Wikstrom, K., Boeree, M. J., Koopmans, P. P., Hekster, Y. A., & Burger, D. M. (2004). Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrobial Agents and Chemotherapy, 48* (5), 1553–1560. https://doi.org/10.1128/AAC.48.5.1553-1560.2004

Li, F., Lu, J., & Ma, X. (2012). CYP3A4-mediated lopinavir bioactivation and its inhibition by ritonavir. *Drug Metabolism and Disposition, 40*(1), 18–24. https://doi.org/10.1124/dmd.111.041400

Li, Q., & Kang, C. B. (2020). Progress in developing inhibitors of SARS-CoV-2 3C-like protease. *Microorganisms, 8* (8), 1250. https://doi.org/10.3390/microorganisms8081250

Li, W., Moore, M. J., Vasilieva, N., Sui, J., Wong, S. K., Berne, M. A., Somasundaran, M., Sullivan, J. L., Luzuriaga, K., Greenough, T. C., Choe, H., & Farzan, M. (2003). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature, 426* (6965), 450–454. https://doi.org/10.1038/nature02145

Li, Z., Tomlinson, A. C., Wong, A. H., Zhou, D., Desforges, M., Talbot, P. J., Benlekbir, S., Rubinstein, J. L., & Rini, J. M. (2019). The human coronavirus HCoV-229E S-protein structure and receptor binding. *eLife*, *8*, e51230. https://doi.org/10.7554/eLife.51230

Meini, S., Pagotto, A., Longo, B., Vendramin, I., Pecori, D., & Tascini, C. (2020). Role of lopinavir/ritonavir in the treatment of Covid-19: A review of current evidence, guideline recommendations, and perspectives.*Journal of Clinical Medicine, 9* (7), 2050. https://doi.org/10.3390/jcm9072050

Nile, S. H., Nile, A., Qiu, J., Li, L., Jia, X., & Kai, G. (2020). COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. *Cytokine & Growth Factor Reviews, 53,* 66–70. https://doi.org/10.1016/j.cytogfr.2020.05.002

Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., Xie, C., Ma, K., Shang, K., Wang, W., & Tian, D.-S. (2020). Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clinical Infectious Diseases, 71* (15), 762–768. https://doi.org/10.1093/cid/ciaa248

Rabi, F. A., Al Zoubi, M. S., Kasasbeh, G. A., Salameh, D. M., & Al-Nasser, A. D. (2020). SARS-CoV-2 and coronavirus disease 2019: What we know so far. *Pathogens, 9* (3), 231. https://doi.org/10.3390/pathogens9030231

Rower, J. E., Meissner, E. G., Jimmerson, L. C., Osinusi, A., Sims, Z., Petersen, T., Bushman, L. R., Wolfe, P., McHutchison, J. G., Kottilil, S., & Kiser, J. J. (2015). Serum and cellular ribavirin pharmacokinetic and concentration–effect analysis in HCV patients receiving sofosbuvir plus ribavirin. *Journal of Antimicrobial Chemotherapy, 70* (8), 2322–2329. https://doi.org/10.1093/jac/dkv122

Sadeghi, A., Ali Asgari, A., Norouzi, A., Kheiri, Z., Anushirvani, A., Montazeri, M., Hosamirudsai, H., Afhami, S., Akbarpour, E., Aliannejad, R., Radmard, A. R., Davarpanah, A. H., Levi, J., Wentzel, H., Qavi, A., Garratt, A., Simmons, B., Hill, A., & Merat, S. (2020). Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): A randomized controlled trial. *Journal of Antimicrobial Chemotherapy, 75* (11), 3379–3385. https://doi.org/10.1093/jac/dkaa334

Sayad, B., Sobhani, M., & Khodarahmi, R. (2020). Sofosbuvir as repurposed antiviral drug against COVID-19: Why were we convinced to evaluate the drug in a registered/approved clinical trial? *Archives of Medical Research, 51* (6), 577–581. https://doi.org/10.1016/j.arcmed.2020.04.018

Setiadi, A. P., Wibowo, Y. I., Halim, S. V., Brata, C., Presley, B., & Setiawan, E. (2020). Tata laksana terapi pasien dengan COVID-19: Sebuah kajian naratif. *Indonesian Journal of Clinical Pharmacy, 9* (1), 70. https://doi.org/10.15416/ijcp.2020.9.1.70

Sigrist, C. J., Bridge, A., & Le Mercier, P. (2020). A potential role for integrins in host cell entry by SARS-CoV-2. *Antiviral Research, 177*, 104759. https://doi.org/10.1016/j.antiviral.2020.104759

Spinner, C. D., Gottlieb, R. L., Criner, G. J., Arribas López, J. R., Cattelan, A. M., Soriano Viladomiu, A., Ogbuagu, O., Malhotra, P., Mullane, K. M., Castagna, A., Chai, L. Y. A., Roestenberg, M., Tsang, O. T. Y., Bernasconi, E., Le Turnier, P., Chang, S. C., Sengupta, D., Hyland, R. H., Osinusi, A. O., & Marty, F. M. (2020). Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: A randomized clinical trial. *JAMA, 324* (11), 1048–1057. https://doi.org/10.1001/jama.2020.16349

Sugitha, K. S. L. (2020). COVID-19: Respon imunologis, ketahanan pada permukaan benda dan pilihan terapi klinis. *Intisari Sains Medis, 11* (2), 791–797. https://doi.org/10.15562/ism.v11i2.746

Sun, D. (2020). Remdesivir for treatment of COVID-19: Combination of pulmonary and IV administration may offer additional benefit. **AAPS Journal, 22* (4), 77. https://doi.org/10.1208/s12248-020-00459-8

Tan, Q., Duan, L., Ma, Y., Wu, F., Huang, Q., Mao, K., Xiao, W., Xia, H., Zhang, S., Zhou, E., Ma, P., Song, S., Li, Y., Zhao, Z., Sun, Y., Li, Z., Geng, W., Yin, Z., & Jin, Y. (2020). Is oseltamivir suitable for fighting against COVID-19: In silico assessment, in vitro and retrospective study. *Bioorganic Chemistry, 104,* 104257. https://doi.org/10.1016/j.bioorg.2020.104257

Tong, S., Su, Y., Yu, Y., Wu, C., Chen, J., Wang, S., & Jiang, J. (2020). Ribavirin therapy for severe COVID-19: A retrospective cohort study. *International Journal of Antimicrobial Agents, 56* (3), 106114. https://doi.org/10.1016/j.ijantimicag.2020.106114

Ulhaq, Z. S., & Soraya, G. V. (2020). Interleukin-6 as a potential biomarker of COVID-19 progression. *Médecine et Maladies Infectieuses, 50 (4)*, 382–383.

https://doi.org/10.1016/j.medmal.2020.04.002

Uzunova, K., Filipova, E., Pavlova, V., & Vekov, T. (2020). Insights into antiviral mechanisms of remdesivir, lopinavir/ritonavir and chloroquine/hydroxychloroquine affecting the new SARS-CoV-2. *Biomedicine & Pharmacotherapy, 131,* 110668. https://doi.org/10.1016/j.biopha.2020.110668

Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J. J. V., Pfeffer, M. A., & Solomon, S. D. (2020). Renin–angiotensin–aldosterone system inhibitors in patients with COVID-19. *New England Journal of Medicine, 382* (17), 1653–1659. https://doi.org/10.1056/NEJMsr2005760

Wang, Y., Anirudhan, V., Du, R., Cui, Q., & Rong, L. (2020). Recent updates in the pharmacological management of COVID-19. *Letters in Applied NanoBioScience, 10* (1), 1969-1980.

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., & Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research, 30* (3), 269–271. https://doi.org/10.1038/s41422-020-0282-0

Wang, Q., Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z., Lu, G., Qiao, C., Hu, Y., Yuen, K.-Y., Wang, Q., Zhou, H., Yan, J., & Qi, J. (2020). Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell, 181* (4), 894-904.e9. https://doi.org/10.1016/j.cell.2020.03.045

Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., Hu, Y., Luo, G., Wang, K., Lu, Y., Li, H., Wang, S., Ruan, S., Yang, C., Mei, C., ... Wang, C. (2020). Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet, 395*(10236), 1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9

World Health Organization. (2020). *Coronavirus disease (COVID-19) pandemic*. https://www.who.int/emergencies/diseases/novel-coronavirus-2019

Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J., & Prescott, H. C. (2020). Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). *JAMA, 324* (8), 782. https://doi.org/10.1001/jama.2020.12839

Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., ... Song, Y. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Internal Medicine, 180* (7), 934. https://doi.org/10.1001/jamainternmed.2020.0994

Wu, C. Y., Jan, J. T., Ma, S. H., Kuo, C. J., Juan, H. F., Cheng, Y. S. E., Hsu, H. H., Huang, H. C., Wu, D., Brik, A., Liang, F. S., Liu, R. S., Fang, J. M., Chen, S. T., Liang, P. H., & Wong, C. H. (2004). Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.0403596101

Wu, Z., & McGoogan, J. M. (2020). Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA, 323* (13), 1239. https://doi.org/10.1001/jama.2020.2648

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., & Wang, F.-S. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine, 8* (4), 420–422. https://doi.org/10.1016/S2213-2600(20)30076-X

Yuki, K., Fujiogi, M., & Koutsogiannaki, S. (2020). COVID-19 pathophysiology: A review. *Clinical Immunology, 215*, 108427. https://doi.org/10.1016/j.clim.2020.108427

Zhou, Y., Fu, B., Zheng, X., Wang, D., Zhao, C., Qi, Y., Sun, R., Tian, Z., Xu, X., & Wei, H. (2020). Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. *National Science Review, 7* (6), 998–1002. https://doi.org/10.1093/nsr/nwaa041

Zou, X., Chen, K., Zou, J., Han, P., Hao, J., & Han, Z. (2020). Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Frontiers of Medicine, 14* (2), 185–192. https://doi.org/10.1007/s11684-020-0754-0

Narrative Review of Anti-Retrovirals Used in COVID-19 Treatment

ORIGINALITY REPORT

29%	19%	26%	11%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	academic.oup.com Internet Source	1%
2	www.spandidos-publications.com Internet Source	1%
3	eprints.aihta.at Internet Source	1%
4	Karuna Chavalertsakul, Yuda Sutherasan, Tananchai Petnak, Kanin Thammavaranucupt et al. "Remdesivir versus Favipiravir in Hospitalized Patients with Moderate to Severe COVID-19 Pneumonia: A Propensity Score-Matched Retrospective Cohort Study", International Journal of General Medicine, 2024 Publication	1%
5	ojs.stfmuhammadiyahcirebon.ac.id Internet Source	1%
6	Igor de Andrade Santos, Victória Riquena Grosche, Fernando Rodrigues Goulart	1%

Bergamini, Robinson Sabino-Silva et al. "Antivirals Against Coronaviruses: Candidate Drugs for SARS-CoV-2 Treatment?", Frontiers in Microbiology, 2020
Publication

7	tdtmvjournal.biomedcentral.com Internet Source	1 %
8	Jayalakshmi Vallamkondu, Albin John, Willayat Yousuf Wani, Suguru Pathinti Ramadevi et al. "SARS-CoV-2 pathophysiology and assessment of coronaviruses in CNS diseases with a focus on therapeutic targets", Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 2020 Publication	1 %
9	Submitted to University of Salford Student Paper	<1 %
10	Cristina Adriana Dehelean, Voichita Lazureanu, Dorina Coricovac, Marius Mioc et al. "SARS-CoV-2: Repurposed Drugs and Novel Therapeutic Approaches—Insights into Chemical Structure—Biological Activity and Toxicological Screening", Journal of Clinical Medicine, 2020 Publication	<1 %
11	Submitted to Case Western Reserve University Student Paper	<1 %

12	Anderson, Thomas K.. "Structural and Functional Approaches to Broaden Our Understanding of Coronavirus Replication Complexes", The University of Wisconsin - Madison, 2024 Publication	<1 %
13	Maen Abdelrahim, Abdullah Esmail, Noor Al Saadi, Eva Zsigmond et al. "Thymoquinone's Antiviral Effects: It is Time to be Proven in the Covid-19 Pandemic Era and its Omicron Variant Surge", Frontiers in Pharmacology, 2022 Publication	<1 %
14	Florence Ader. "Protocol for the DisCoVeRy trial: multicentre, adaptive, randomised trial of the safety and efficacy of treatments for COVID-19 in hospitalised adults", BMJ Open, 2020 Publication	<1 %
15	Stefano Romagnoli, Adriano Peris, A. Raffaele De Gaudio, Pierangelo Geppetti. "SARS-CoV-2 and COVID-19: From the Bench to the Bedside", Physiological Reviews, 2020 Publication	<1 %
16	Submitted to University of Queensland Student Paper	<1 %
17	www.preprints.org Internet Source	<1 %

18	Afra Rezagholizadeh, Sajad Khiali, Parvin Sarbakhsh, Taher Entezari-Maleki. "Remdesivir for treatment of COVID-19; an updated systematic review and meta-analysis", European Journal of Pharmacology, 2021 Publication	<1 %
19	Koichi Yuki, Miho Fujiogi, Sophia Koutsogiannaki. "COVID-19 pathophysiology: A review", Clinical Immunology, 2020 Publication	<1 %
20	eprints.iums.ac.ir Internet Source	<1 %
21	Hazael Ramiro Ceja-Gálvez, Francisco Israel Renteria-Flores, Ferdinando Nicoletti, Jorge Hernández-Bello et al. "Severe COVID-19: Drugs and Clinical Trials", Journal of Clinical Medicine, 2023 Publication	<1 %
22	Submitted to Intercollege Student Paper	<1 %
23	Nida Bokharee, Yusra Habib Khan, Aisha Khokhar, Tauqeer Hussain Mallhi, Nasser Hadal Alotaibi, Maria Rasheed. "Pharmacological interventions for COVID-19: a systematic review of observational studies	<1 %

and clinical trials", Expert Review of Anti-infective Therapy, 2021
Publication

24	Roberta Monardo, Andrea Mastrangelo, Laura Galli, Alessandro Tomelleri et al. "Real-life use of high-dose anakinra in patients with COVID-19 treated with remdesivir", Future Virology, 2024 Publication	<1 %
25	Zohreh Rezaei, Leila Mobasheri, Farzad Sadri. "Molecular Insights into COVID-19 Pathophysiology, Immune Pathogenesis, Detection, and Treatment", DNA and Cell Biology, 2021 Publication	<1 %
26	bmcpsychiatry.biomedcentral.com Internet Source	<1 %
27	pure.royalholloway.ac.uk Internet Source	<1 %
28	www.springermedizin.de Internet Source	<1 %
29	Submitted to Massey University Student Paper	<1 %
30	Submitted to University System of Georgia Student Paper	<1 %
31	Submitted to University of Brighton Student Paper	

		<1%
32	Submitted to University of Malaya Student Paper	<1%
33	jgeb.springeropen.com Internet Source	<1%
34	www.dovepress.com Internet Source	<1%
35	Batu Özlüşen, Şima Kozan, Rüştü Emre Akcan, Mekselina Kalender et al. "Effectiveness of favipiravir in COVID-19: a live systematic review", European Journal of Clinical Microbiology & Infectious Diseases, 2021 Publication	<1%
36	S Kana Saputra, Insan Taufik, Mhd Hidayat, Dinda Farahdilla Dharma. "Pneumonia identification based on lung texture analysis using modified k-nearest neighbour", Journal of Physics: Conference Series, 2022 Publication	<1%
37	Submitted to University of Auckland Student Paper	<1%
38	f6publishing.blob.core.windows.net Internet Source	<1%
39	Fatemeh Ahmadi, Sasan Moogahi, Marya Cheraghi, Farid Yousefi, Zahra Fakhraei.	<1%

	"Determination of the Efficacy of Daclatasvir Plus Sofosbuvir in Patients with Acute Respiratory Coronavirus Syndrome (SARS-COV-2): A Randomized Clinical Trial", Journal of Iranian Medical Council, 2022 Publication	
40	Submitted to King's College Student Paper	<1 %
41	Submitted to University of Southampton Student Paper	<1 %
42	Burhan Ul Haque Sheikh, Aasim Zafar. "White-box inference attack: compromising the security of deep learning-based COVID-19 diagnosis systems", International Journal of Information Technology, 2023 Publication	<1 %
43	Submitted to Krida Wacana Christian University Student Paper	<1 %
44	Mitrasadat Rezaei, Seyed Ali Ziai, Sajad Fakhri, Ramin Pouriran. "ACE2: Its potential role and regulation in severe acute respiratory syndrome and COVID-19", Journal of Cellular Physiology, 2020 Publication	<1 %
45	Submitted to University College London Student Paper	<1 %

46	Submitted to University of Keele Student Paper	<1 %
47	ibdigital.uib.es Internet Source	<1 %
48	www.diva-portal.org Internet Source	<1 %
49	Submitted to Central Queensland University Student Paper	<1 %
50	Charlotte Hedskog, Christoph D. Spinner, Ulrike Protzer, Dieter Hoffmann et al. "No Remdesivir Resistance Observed in the Phase 3 Severe and Moderate COVID-19 SIMPLE Trials", Viruses, 2024 Publication	<1 %
51	Dennis C. Copertino, Bruno C. Casado Lima, Rodrigo R. R. Duarte, Timothy R. Powell et al. "Antiretroviral drug activity and potential for pre-exposure prophylaxis against COVID-19 and HIV infection", Journal of Biomolecular Structure and Dynamics, 2021 Publication	<1 %
52	Hamideh Abbaspour Kasgari, Siavash Moradi, Amir Mohammad Shabani, Farhang Babamahmoodi et al. "Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized	<1 %

COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial", Journal of Antimicrobial Chemotherapy, 2020
Publication

53	Submitted to Indiana University Student Paper	<1%
54	Jackson, A., A. Hill, R. Puls, L. Else, J. Amin, D. Back, E. Lin, S. Khoo, S. Emery, R. Morley, B. Gazzard, and M. Boffito. "Pharmacokinetics of plasma lopinavir/ritonavir following the administration of 400/100 mg, 200/150 mg and 200/50 mg twice daily in HIV-negative volunteers", Journal of Antimicrobial Chemotherapy, 2011. Publication	<1%
55	Margaret A Johnson. "A Once-Daily Lopinavir/Ritonavir-Based Regimen Provides Noninferior Antiviral Activity Compared With a Twice-Daily Regimen", JAIDS Journal of Acquired Immune Deficiency Syndromes, 10/2006 Publication	<1%
56	Seyed Sajad Hosseini Balef, Zohreh Karimi, Ala Azari, Seyed Sadeq Sadraie et al. "A Recent Update on the Clinical Trials and Effectiveness of Drugs Used in COVID-19,	<1%

MERS and SARS Coronaviruses", Anti-Infective Agents, 2022
Publication

57	Submitted to University of Liverpool Student Paper	<1%
58	Submitted to University of Western Sydney Student Paper	<1%
59	Oztas, Deniz yasar. "Drug Repurposing for Covid-19 Using Molecular Docking Tools", Chapman University, 2021 Publication	<1%
60	Xinlei Li, Tao Peng. "Strategy, Progress, and Challenges of Drug Repurposing for Efficient Antiviral Discovery", Frontiers in Pharmacology, 2021 Publication	<1%
61	jamanetwork.com Internet Source	<1%
62	www.rsdjournal.org Internet Source	<1%
63	Abhinav Choubey, Budheswar Dehury, Sunil Kumar, Bikash Medhi, Prosenjit Mondal. "Naltrexone a potential therapeutic candidate for COVID-19", Journal of Biomolecular Structure and Dynamics, 2020 Publication	<1%

64 Feras Jirjees, Ali K Saad, Zahraa Al Hano, Taher Hatahet, Hala Al Obaidi, Yahya H Dallal Bashi. "COVID-19 Treatment Guidelines: Do They Really Reflect Best Medical Practices to Manage the Pandemic?", Infectious Disease Reports, 2021 <1%
Publication

65 K. G. Arun, C. S Sharanya, J. Abhithaj, Dileep Francis, C. Sadasivan. "Drug repurposing against SARS-CoV-2 using E-pharmacophore based virtual screening, molecular docking and molecular dynamics with main protease as the target", Journal of Biomolecular Structure and Dynamics, 2020 <1%
Publication

66 Madeleine E. Laughon, Jacob K. Johnson, Rachel G. Greenberg, Reese H. Clark, Wesley M. Jackson. "Methylxanthine use in infants with hypoxic-ischemic encephalopathy: a retrospective cohort study", Scientific Reports, 2024 <1%
Publication

67 Mansour Amin, Mahnaz Nosratabadi, Seifollah Mohseni, Javad Moazen et al. "Effects of Shallomin with Lopinavir/Ritonavir on clinical outcomes and mortality in COVID-19 patients: A randomised double-blind <1%

clinical trial study", Journal of Herbal Medicine, 2023
Publication

68	Muthmainah, Hanik Badriyah Hidayati, Budi Yanti. "Improving Health for Better Future Life: Strengthening from Basic Science to Clinical Research", CRC Press, 2023 Publication	<1 %
69	boris.unibe.ch Internet Source	<1 %
70	dev.physiciansweekly.com Internet Source	<1 %
71	encyclopedia.pub Internet Source	<1 %
72	files.covid19treatmentguidelines.nih.gov Internet Source	<1 %
73	riu.austral.edu.ar Internet Source	<1 %
74	Maricar Malinis, Dayna McManus, Matthew Davis, Jeffrey Topal. "An overview on the use of antivirals for the treatment of patients with COVID19 disease", Expert Opinion on Investigational Drugs, 2020 Publication	<1 %
75	Pramod Kumar, Anand Kulkarni, Mithun Sharma, Padaki Nagaraja Rao. "Repurposing	<1 %

Hepatitis C Direct -acting antivirals against COVID-19", Journal of Clinical and Experimental Hepatology, 2020
Publication

---

76 Saad Alhumaid, Abbas Al Mutair, Zainab Al Alawi, Naif Alhmeed, Abdul Rehman Zia Zaidi, Mansour Tobaiqy. "Efficacy and Safety of Lopinavir/Ritonavir for Treatment of COVID-19: A Systematic Review and Meta-Analysis", Tropical Medicine and Infectious Disease, 2020 <1%
Publication

---

77 Sherif Abbass, Ehab Kamal, Mohsen Salama, Tary Salman et al. "Efficacy and safety of sofosbuvir plus daclatasvir or ravidasvir in patients with COVID-19: A randomized controlled trial", Journal of Medical Virology, 2021 <1%
Publication

---

78 Tamil Selvan, Miruthula. "Immunopathogenesis of SARS-CoV-2 Variants in a Feline Model", Oklahoma State University, 2024 <1%
Publication

---

79 Zeenat A Shyr, Kirill Gorshkov, Catherine Z Chen, Wei Zheng. " ", Journal of Pharmacology and Experimental Therapeutics, 2020 <1%
Publication

80	bsdwebstorage.blob.core.windows.net Internet Source	<1 %
81	cmr.asm.org Internet Source	<1 %
82	dergipark.org.tr Internet Source	<1 %
83	discovery.ucl.ac.uk Internet Source	<1 %
84	dspace.nplg.gov.ge Internet Source	<1 %
85	funsalud.org.mx Internet Source	<1 %
86	libweb.kpfu.ru Internet Source	<1 %
87	onderzoekmetmensen.nl Internet Source	<1 %
88	opus4.kobv.de Internet Source	<1 %
89	repository.publisso.de Internet Source	<1 %
90	researchopenworld.com Internet Source	<1 %
91	sauyayinlari.sakarya.edu.tr Internet Source	<1 %

92	www.mims.com Internet Source	<1%
93	www.thefreelibrary.com Internet Source	<1%
94	Aristides Tsatsakis, Daniela Calina, Luca Falzone, Dimitrios Petrakis et al. "SARS-CoV-2 pathophysiology and its clinical implications: An integrative overview of the pharmacotherapeutic management of COVID-19", Food and Chemical Toxicology, 2020 Publication	<1%
95	Chris De Savi, David L Hughes, Lisbet Kvaerno. "Quest for a COVID-19 Cure by Repurposing Small Molecule Drugs: Mechanism of Action, Clinical Development, Synthesis at Scale, and Outlook for Supply", Organic Process Research & Development, 2020 Publication	<1%
96	Chuan-Feng Tang, Hong Ding, Rui-Qing Jiao, Xing-Xin Wu, Ling-Dong Kong. "Possibility of magnesium supplementation for supportive treatment in patients with COVID-19", European Journal of Pharmacology, 2020 Publication	<1%
97	Ellen Weisberg, Martin Sattler, Priscilla L Yang, Alexander Parent, Nathanael Gray, James D	<1%

Griffin. "Current Therapies Under Investigation for COVID-19", Canadian Journal of Physiology and Pharmacology, 2020
Publication

---

98 Jienchi Dorward, Oghenekome Gbinigie, Ting Cai, Nia W Roberts, Nigel Garrett, Gail Hayward, Christopher C Butler. "The Protease Inhibitor Lopinavir, Boosted with Ritonavir, as Treatment for COVID-19: A Rapid Review", Antiviral Therapy, 2019 <1%
Publication

---

99 Muhammad Taher, Noratika Tik, Deny Susanti. "Drugs intervention study in COVID-19 management", Drug Metabolism and Personalized Therapy, 2021 <1%
Publication

---

100 Praveen Mathews Varghese, Anthony G. Tsolaki, Hadida Yasmin, Abhishek Shastri et al. "Host-pathogen interaction in COVID-19: Pathogenesis, potential therapeutics and vaccination strategies", Immunobiology, 2020 <1%
Publication

---

101 Rea-Moreno, Martha Gisella. "Attenuating Cytokine Storm Initiation Caused by Influenza and SARS-CoV-2 Using hPSC-Derived Lung Organoids", Icahn School of Medicine at Mount Sinai, 2024 <1%
Publication

102	Saurov Mahanta, Purvita Chowdhury, Neelutpal Gogoi, Nabajyoti Goswami et al. " Potential anti-viral activity of approved repurposed drug against main protease of SARS-CoV-2: an based approach ", Journal of Biomolecular Structure and Dynamics, 2020 Publication	<1 %
103	Yin-Qiu Huang, Sheng-Quan Tang, Xiao-Lei Xu, Yan-Ming Zeng et al. "No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon-Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon-Alpha in Patients With Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective Study", Frontiers in Pharmacology, 2020 Publication	<1 %
104	dokumen.pub Internet Source	<1 %
105	ijpr.sbmu.ac.ir Internet Source	<1 %
106	iris.paho.org Internet Source	<1 %
107	jzs.univsul.edu.iq Internet Source	<1 %

108	platcovid.com Internet Source	<1%
109	sph.nus.edu.sg Internet Source	<1%
110	Federica Duca, Sarah Meny-Gibert. "State–Society Relations around the World through the Lens of the Covid-19 Pandemic - Rapid Test", Routledge, 2023 Publication	<1%
111	Ferreira, Victor Leonel Vieira. "SARS-CoV-2 Detection Methods: Where are we Now?", Universidade de Coimbra (Portugal), 2024 Publication	<1%
112	Hossein Abolhassani, Ghazal Bashiri, Mahdi Montazeri, Hasan Kouchakzadeh, Seyed Abbas Shojaosadati, Seyed Ehsan Ranaei Siadat. "Chapter 2 Ongoing Clinical Trials and the Potential Therapeutics for COVID-19 Treatment", Springer Science and Business Media LLC, 2021 Publication	<1%
113	Madhura Punekar, Manas Kshirsagar, Chaitanya Tellapragada, Kanchankumar Patil. "Repurposing of antiviral drugs for COVID-19 and impact of repurposed drugs on the nervous system", Microbial Pathogenesis, 2022 Publication	<1%

114	Thomas T. Yoshikawa, Shobita Rajagopalan. "Antibiotic Therapy for Geriatric Patients", CRC Press, 2005 Publication	<1 %
115	Zhonglei Wang, Liyan Yang. "Turning the Tide: Natural Products and Natural-Product-Inspired Chemicals as Potential Counters to SARS-CoV-2 Infection", Frontiers in Pharmacology, 2020 Publication	<1 %
116	Chih-Chia Lu, Mei-Yu Chen, Wan-Shin Lee, Yuh-Lih Chang. "Potential therapeutic agents against COVID-19: What we know so far", Journal of the Chinese Medical Association, 2020 Publication	<1 %
117	Christoph D. Spinner, Robert L. Gottlieb, Gerard J. Criner, José Ramón Arribas López et al. "Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19", JAMA, 2020 Publication	<1 %
118	Fran Robson, Khadija Shahed Khan, Thi Khanh Le, Clément Paris, Sinem Demirbag, Peter Barfuss, Palma Rocchi, Wai-Lung Ng. "Coronavirus RNA proofreading: molecular basis and therapeutic targeting", Molecular Cell, 2020	<1 %

Publication

119	Munazza Shahid, Syed Shahzad-ul-Hussan. "Structural insights of key enzymes into therapeutic intervention against SARS-CoV-2", Journal of Structural Biology, 2021 Publication	<1 %
120	Niloufar Najar Nobari, Farnoosh Seirafianpour, Farzaneh Mashayekhi, Azadeh Goodarzi. " A systematic review on treatment-related mucocutaneous reactions in -19 patients ", Dermatologic Therapy, 2020 Publication	<1 %
121	Shahamah Jomah, Syed Mohammed Basheeruddin Asdaq, Mohammed Jaber Al-Yamani. "Clinical efficacy of antivirals against novel coronavirus (COVID-19): A review", Journal of Infection and Public Health, 2020 Publication	<1 %
122	Sun Bean Kim, Seungeun Ryoo, Kyungmin Huh, Eun-Jeong Joo et al. "Revised Korean Society of Infectious Diseases/National Evidence-based Healthcarea Collaborating Agency Guidelines on the Treatment of Patients with COVID-19", Infection & Chemotherapy, 2021 Publication	<1 %
123	Yoshinori Mine, Vincent Guyonnet, Hajime Hatta, Françoise Nau, Ning Qiu. "Handbook	<1 %

of Egg Science and Technology", CRC Press, 2023
Publication

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

Narrative Review of Anti-Retrovirals Used in COVID-19 Treatment

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13

PAGE 14

PAGE 15

PAGE 16

PAGE 17