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REVIEW ARTICLE

Drugs and natural products for the treatment of COVID-19 during 2020, the first year of the pandemic

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Abstract

This work aimed to show which treatments showed efficacy against coronavirus disease 2019 (COVID-19); therefore, the results of 37 clinical trials started in 2020 and completed in 2021 are reviewed and discussed here. These were selected from databases, excluding vaccines, computational studies, in silico, in vitro, and those with hyperimmune sera from recovered patients. We found 34 drugs, one vitamin, and one herbal remedy with pharmacological activity against symptomatic COVID-19. They reduced mortality, disease progression, or recovery time. For each treatment, the identifier and type of trial, the severity of the disease, the sponsor, the country where the trial was conducted, and the trial results are presented. The drugs were classified according to their mechanism of action. Several drugs that reduced mortality also reduced inflammation in the most severe cases. These include some that are not considered anti-inflammatory, such as Aviptadil, pyridostigmine bromide, anakinra, imatinib, baricitinib, and bevacizumab, as well as the combination of ivermectin, aspirin, dexamethasone, and enoxaparin. Nigella sativa seeds with honey have also been reported to have therapeutic activity. On the other hand, tofacitinib, novaferon with ritonavir, and lopinavir were also effective, as well as in combination with antiviral therapies such as danoprevir with ritonavir. The natural products colchicine and Vitamin D3 were only effective in patients with mild-to-moderate COVID-19, as was hydroxychloroquine. Drug repositioning has been the main tool in the search for effective therapies by expanding the pharmacological options available to patients.

Keywords: *Severe acute respiratory syndrome coronavirus 2. Coronavirus disease 2019. Clinical studies. Anti-inflammatory. Antiviral repositioning.*

Fármacos y productos naturales para el tratamiento de la COVID-19 durante 2020, el primer año de la pandemia

Resumen

El objetivo del presente trabajo fue conocer qué tratamientos mostraron efectividad contra COVID-19, para lo cual se revisan y discuten los resultados de 37 estudios clínicos iniciados durante 2020 y concluidos en 2021. Estos fueron seleccionados de bases de datos, excluyendo vacunas, estudios computacionales, in silico, in vitro y con sueros hiperinmunes de pacientes recuperados. Se documentaron 34 fármacos, una vitamina y un remedio herbolario, con actividad farmacológica ante COVID-19 sintomático. Estos redujeron la mortalidad, el progreso de la enfermedad, o el tiempo de recuperación. Para cada

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tratamiento se presenta identificador y tipo de estudio, la gravedad de la enfermedad, patrocinador, país donde se realizó, así como sus resultados. Los fármacos se clasificaron de acuerdo con su mecanismo de acción. Varios fármacos que redujeron la mortalidad también disminuyeron la inflamación en los casos más graves. Esto incluyendo algunos no considerados antiinflamatorios, como el aviptadil, el bromuro de piridostigmina, el anakinra, el imatinib, el baricitinib y el bevacizumab, así como la combinación de ivermectina, aspirina, dexametasona y enoxaparina. También se reportaron con actividad terapéutica las semillas de Nigella sativa con miel. Además, resultaron efectivos el tofacitinib, el novaferón con ritonavir y lopinavir, así como los antivirales en terapias combinadas como el danoprevir con ritonavir. Los productos naturales colchicina y vitamina D3, solo tuvieron actividad en los pacientes en estado leve a moderado de la COVID-19, así como la hidroxicloroquina. El reposicionamiento de fármacos fue la principal herramienta para buscar terapias efectivas ampliando las opciones farmacológicas accesibles a los pacientes.

Palabras clave: *SARS-CoV-2. COVID-19. Estudios clínicos. Antiinflamatorios. Reposicionamiento antiviral.*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the coronavirus that causes the infectious disease known as coronavirus disease 2019 (COVID-19). Its global spread led the WHO to declare it a public health emergency of international concern. SARS-CoV-2 is the seventh zoonotic coronavirus to infect humans. Its RNA genome is 80% similar to that of SARS-CoV[1]. It encodes several structural proteins, including spike (S), which regulates viral entry by binding to angiotensin-converting enzyme 2 (ACE2). This cellular receptor is expressed in respiratory epithelium, vascular endothelium, alveolar monocytes, and macrophages, among others[2].

The binding of ACE2 and S proteins triggers a membrane fusion reaction initiated by transmembrane serine protease 2 by cleaving S protein. Subsequently, the virus enters the cell by clathrin-mediated endocytosis[3] and its genetic material is released into the cytosol where it is translated into non-structural and structural proteins. The former assemble in membranes derived from the endoplasmic reticulum and replicate viral RNA. The latter assemble into viral particles and exit the cell through the lysosomal pathway[4].

During infection, the SARS-CoV-2 virus primarily enters type II pneumocytes, where an innate immune response is initiated. Macrophages initiate this response in the pulmonary alveoli, which secrete mediators such as tumor necrosis factor (TNF) and recruit lymphocytes and neutrophils, which release proinflammatory cytokines (interleukin [IL]-1, IL-6, and IL-8) and reactive oxygen species on entry into the alveoli[2].

SARS-CoV-2 can also infect monocytes, macrophages, dendritic cells, and lymphocytes. These cell lines in severe COVID-19 undergo dysregulated cytokine release, or "cytokine storm" syndrome, which dramatically increases leukocyte recruitment and causes endothelial cell and pneumocyte injury. This leads to pulmonary capillary leakage and surfactant abnormalities that compromise alveolar gas exchange, resulting in acute respiratory distress syndrome, multi-organ failure, and, in the worst case, death[2].

As of December 2020, COVID-19 disease had a global case fatality rate of 2.3% and a case fatality rate of 8.8% in Mexico[5]. COVID-19 is a systemic disease that presents with asymptomatic or presymptomatic infection. In symptomatic patients, mild, moderate, severe, very severe and critical disease occurs, as described in table 1, with the most common symptoms being fever, cough, dyspnea, and loss of smell and taste[6,7].

During the 1st year of the pandemic, management of COVID-19 included infection control measures, symptom management, and intensive care support for severe or critical illness[1]. However, clinical trials were also initiated, starting with drug repositioning. As a result of the tremendous effort and guidance on clinical management strategies to deal with COVID-19, numerous clinical trials were completed; however, they encountered various problems, including several that were never completed due to difficulties in patient recruitment or follow-up.

At present, despite the availability of various types of RNA- and DNA-based vaccines, it is still necessary to develop effective therapies to prevent severe cases of COVID-19 and death. For example, in 2022, the mortality rate was 4.7% in Mexico and 1% worldwide[6]. This review identified drugs that showed efficacy in clinical trials for treating SARS-Cov-2 and COVID-19 disease during the 1st year of the pandemic.

Many natural and synthetic compounds have been described and suggested in databases as potential inhibitors of COVID-19 development and progression. However, many of the compound repositioning studies have been performed by *in silico* computational studies without being supported by *in vitro*, *in vivo*, or clinical

Table 1. Clinical phases of COVID-19

Clinical phases	Symptoms	Symptom management
Mild	Fever, cough, altered sense of smell or taste, fatigue, myalgia or arthralgia, expectoration, chest pain, without evidence of pneumonia	Antipyretic/analgesic Outpatient
Moderate	Lower respiratory tract disease. Radiological evidence of pneumonia	Antibiotics. Hospitalized, no oxygen requirement
Severe	Pneumonia, RR > 30, SpO_2 < 90% PI > 50% (PaO_2/ FiO_2) < 300 mmHg	Venous thromboembolism prophylaxis, antibiotics, and corticosteroids. Without oxygen therapy or with low flow
Very severe	PaO_2/FiO_2 < 200 mmHg Hyperinflammation, acute respiratory distress syndrome	Antimicrobial treatment, venous thromboembolism prophylaxis, and pulmonary vasodilator. Non-invasive or high flow oxygenation. Intensive care unit
Critical	Acute respiratory distress syndrome, sepsis, hypoxemic respiratory failure and hemodynamic instability, hypercoagulability, and multiorgan failure. PaO_2/FiO_2 < 150 mmHg	Antimicrobial treatment, venous thromboembolism prophylaxis, pulmonary vasodilator, corticosteroids, endotracheal intubation, and mechanical ventilation. Intensive care unit

COVID-19: coronavirus disease 2019; PaO_2/FiO_2: ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PI: pulmonary infiltrates; RR: respiratory rate measured in breaths per minute; SpO_2: blood oxygen saturation levels[7,8].

studies to demonstrate their activity. Therefore, such results were excluded from the present review. Similarly, papers on the use of hyperimmune immunoglobulin from patients who have developed COVID-19 disease were excluded due to the complexity of evaluating each patient from whom the anti-SARS-CoV-2 sera were obtained. Studies related to vaccine development were also excluded because this type of biologic is classified as a prophylactic treatment rather than a drug for treating patients with COVID-19.

Methods

A search was performed in specialized databases available at UNAM and open access databases, using the following search strategy in the Title, Abstract, and Keywords fields: (sars AND cov 2 AND inhibitor AND NOT [docking OR *"in silico"* OR "virtual screening" OR computational OR antibody OR antibodies OR plasma OR "network model" OR immunoinformatics OR epitope]).

The following types of studies were included in this work: Adaptive clinical, randomized, non-randomized, cross-assignment, placebo, blinded, double-blind, triple-blind, quadruple-blind, exploratory, interventional, longitudinal, observational, parallel, prospective, retrospective, single-center, multicenter, single-group, and triple-group studies describing the activity of drugs against SARS-CoV-2 and COVID-19 and their effect on reducing mortality, respiratory failure, viral load, disease progression, hospitalization, or recovery time. Only full-length articles in English and Spanish in which the study started between December 31, 2019, and December 31, 2020, were considered, and the results of these studies were reviewed until November 01, 2021. The search procedure is shown in Fig. 1.

After obtaining a total of 1387 articles, we eliminated duplicates, leaving a total of 991 unique articles. A selection was then made based on the title and abstract, excluding studies related to hyperimmune sera from recovered patients and those focused on vaccine development. Computational, *in silico*, and *in vitro* studies were also excluded because they used different terms to define the type of research, making it difficult to identify them using Boolean operators. In the final screening stage, 152 relevant articles were identified. However, 90 studies that were not completed by November 2021 and 25 drug-related studies that showed no activity were excluded. As a result, a total of 37 articles were included in this review.

Results

Effective treatments

Drugs, an herbal remedy, and a vitamin were documented; 24 were used alone, and 12 in combination with others. These successfully reduced mortality, hospitalization, respiratory failure, viral load, disease progression, or recovery time in patients with COVID-19. Most are available internationally and have been identified in

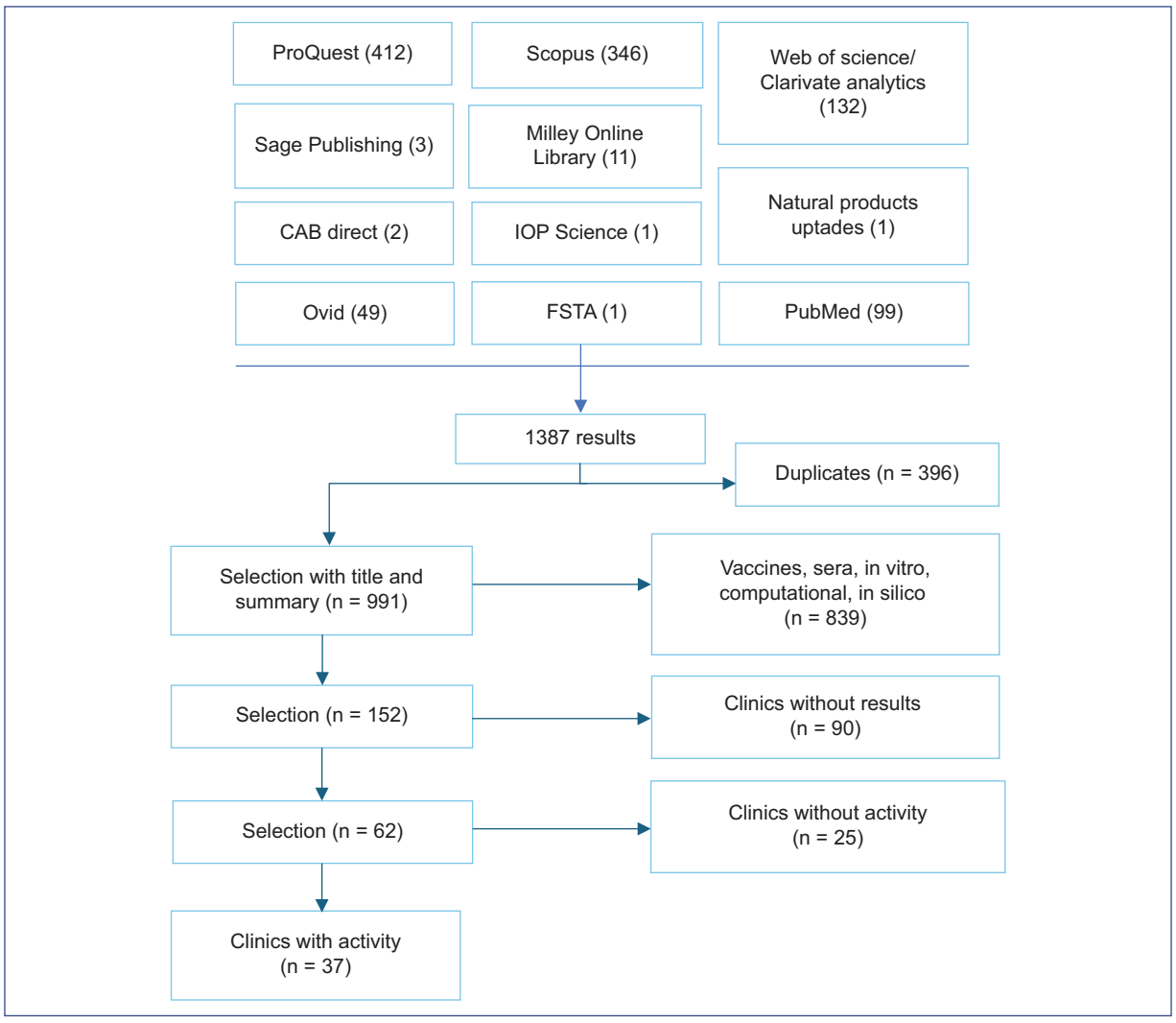

Figure 1. Summary of the design for articles selection and results.

repositioning studies. Table 2 lists the drugs, vitamins, and remedies that were administered individually, while table 3 lists the combined therapies. For each treatment, the identifier and type of trial, the severity of the disease, the sponsor and country in which the trial was conducted, and the trial results are presented.

Among the therapies that promoted clinical improvement, we highlight those that reduced the rate or probability of death by 50% or more in patients with severe, very severe, or critical illness. Aviptadil reduced mortality by 50% in critically ill patients. While in patients with very severe disease, the reduction in the rate of mortality was in first place bevacizumab (no mortality), in second place the combination of ivermectin, dexamethasone, aspirin, and enoxaparin (71%), and in third place pyridostigmine bromide (63.3%). In severe patients, *Nigella sativa* seeds with honey also reduced mortality (~70%), followed by low-molecular-weight heparin (64%), the combination therapy of hydroxychloroquine with favipiravir, darunavir, and ritonavir (16-4%), baricitinib (50% and 58% with corticosteroids) and anakinra (50%), as well as the combination of hydroxychloroquine, favipiravir, darunavir, and ritonavir (25%). We also highlight tocilizumab as it significantly reduced the time to clinical discharge (at day 4) (Tables 2 and 3).

However, given that the disease develops in two phases, an initial phase of high viral replication and a second phase of inflammation[7,8], controlling the infection before the hyperinflammatory response is triggered is important. Therefore, we highlight the activity of those treatments that, in mild-to-moderate disease, promoted patient recovery before seven days or significantly reduced viral load, such as danoprevir with ritonavir, hydroxychloroquine with oseltamivir,

Table 2. Clinical studies of individually administered drugs against COVID-19 that showed effectiveness

Drug	Study identifier	Type of study	Sponsor/Country of study	Phase, (Patients), Severity	Results	References
Acalabrutinib	NCT00001467; NCT01200953	IN	Astra Zeneca/US	(19) Severe	Improved lung function and decreased inflammation	47
Anakinra* (Kineret)	NCT04357366	OG, NoR, OL		II (1000) Severe	Reduced respiratory failure and mortality by 50%	11
Aviptadil (Zyesami)	NCT04311697	R, PL, MC	NeuroRx, Inc/US	II (196) Critical	Reduced respiratory failure and mortality	10
Baricitinib	NCT04393051	IN/NRC	Azienda Ospedaliero U. Pisana/ IT	II (126) Moderate-Severe	Reduced inflammation, viral load, clinical worsening, and mortality	38
Bevacizumab*	NCT04275414	IN, OG, OL	Qilu Hospital, Renmin Hospital of Wuhan/CN, IT	II (27) Severe, very severe	Reduced fever, duration of oxygen support, and mortality	70
Pyridostigmine bromide	NCT04343963	IN, R, QB, PL	Instituto Nacional Salvador Zubirán/ MX	II (436) Very severe	Reduced the need for mechanical ventilation and mortality	15
Chloroquine	NCT04323527	IN, R, DB	Fundação Medicina Tropical Dr. H. V. /BR	IIb (81) Critical	At low doses, CQ decreased mortality	19
Colchicine†	NCT04322682	IN, R, DB, PL	Montreal Heart Institute/CA	III (4488) Mild	Reduced mortality and hospital admissions	31
Eculizumab*	NCT04346797	R, PR, OL, OG	Publique Hopitaux de Paris/ FR	II (8) Severe	Six patients improved significantly	32
Favipiravir	CTRI/2020/05/025114	OL, R, OG, PR, MC, TE	IN	III (150) Mild-moderate	The duration of clinical signs and symptoms decreased	61
Favipiravir versus umifenovir	ChiCTR2000030254	PS, OL, MC, R	CN	(240) Moderate	Higher patient recovery rate at day 7 with favipiravir	62
Fluvoxamine	NCT04342663	DB, R, PL	Washington University/ US	II (152) Mild	Reduced disease progression	21
Nitric oxide gas	NCT04305457	IN, R, OL, TE.	Massachusetts General Hospital/ US	II (29) Severe	Reduced respiratory distress and prevented readmissions	72
LMWH	NCT04323761	OB, PS	University Hospital of Pisa/IT	(244) Moderate-severe	Reduced risk of disease progression and mortality	24
Imatinib mesylate	EudraCT 2020-001236-10	IN	Amsterdam Medical Center Foundation/ NL	(385) Very severe	Reduced mortality and duration of mechanical ventilation	37
Nigella sativa oil‡	NCT04401202	IN, R, PR, PS	King Abdulaziz University/SA	II (183) Mild	Significantly reduced recovery time	27

(Continues)

Table 2. Clinical studies of individually administered drugs against COVID-19 that showed effectiveness *(continued)*

Drug	Study identifier	Type of study	Sponsor/Country of study	Phase, (Patients), Severity	Results	References
Nigella sativa and honey‡	NCT04347382	IN, R, PR, PL	Sohaib Ashraf/ PK	III (313) Moderate-severe	Reduced symptoms, viral load, and mortality rate	26
Opaganib	NCT04414618	IN, R, PR, PL.	RedHill Biopharma Limited/US, IL	II (42) Severe	Reduced supplemental oxygen requirement	51
Ravulizumab*	NCT04369469	IN, R, PR, OL	Alexion Pharma /US	III (22) Severe	Reduced terminal complement C5 convertase	34
Remdesivir	NCT04292730	IN, R, PR, OL, ST	Gilead Sciences/ US, CN, FR, DE, HK, IT, JP, KR, NL, SG, ES, SE, CH, TW, GB	III (584) Moderate	The 5-day treatment improved the clinical condition	57
Remdesivir	NCT04280705	IN, R, DB, PL.	Europe, Asia, and America	III (1062) Moderate-Severe	Reduced recovery time	23
Talidomide	NCT04273529	R, PR, QB	H. Wenzhou Medical University/ CN.	II (12) Critical	Recovery in half the time of the control group	17
Tocilizumab*	NCT04331795	NoR, OG, OL	University of Chicago/ US	II (32) Severe	It was associated with clinical and laboratory improvement in patients	22
Tofacitinib	NCT04469114	R, PL, PR	Albert Einstein Israelite Hospital / BR	III (289) Moderate	Reduced mortality	44
Umifenovir		PS, NoR	CN	(62) Mild	Reduced symptoms of fever, cough	63
Vitamin D_3†	NCT04560608	Quasi-experimental	Angers University Hospital/FR	(77) Moderate	Reduced disease progression and mortality	75

*Biologics.
†Natural products or their semi-synthetic derivatives.
‡Herbal remedy.
COVID-19: coronavirus disease 2019; DB: double-blind; IN: interventional; MC: multicenter; NoR: non-randomized; NRC: non-recruiting; OB: observational; OG: one group; OL: open-label; PL: placebo; PR: parallel; PS: prospective; QB: quadruple-blind; R: randomized; ST: standard therapy; TB: triple-blind; SA: Saudi Arabia; BR: Brazil; CA: Canada; CH: Switzerland; CN: China; DE: Germany; ES: Spain; FR: France; GB: United Kingdom; GR: Greece; HK: Hong Kong; IN: India; IL: Israel; IT: Italy; JP: Japan; KR: South Korea; MX: Mexico; NL: Netherlands; PK: Pakistan; SE: Sweden; SG: Singapore; TW: Taiwan; US: United States; LMWH: low-molecular-weight heparin.

the combination of baricitinib with lopinavir and ritonavir, multidrug therapy with lopinavir, ritonavir, interferon (IFN) β-1b, and ribavirin, in addition to, umifenovir, favipiravir, novaferon, tofacitinib, and colchicine (Tables 2 and 3).

Mechanism of action

Regarding the mechanism of action of the drugs, vitamins, and natural products that have shown efficacy in clinical trials have been found to act by inhibiting cytokine release, inflammation, tubulin polymerization, complement system, tyrosine kinases, viral replication, thrombosis, chemotaxis, or promote bronchodilation, or are regulators of innate and adaptive immunity. They are presented below according to their biological activity.

Anti-inflammatory drugs that regulate the release of proinflammatory cytokines

Aviptadil (Zyesami) is a vasodilator neuropeptide with anti-inflammatory and immunomodulatory activity. It binds to the vasoactive intestinal peptide (VIP) receptor type 1

Table 3. Clinical studies of combination therapies against SARS-CoV-2 and COVID-19 that showed efficacy against the disease

Drug	Study identifier	Type of study/ Status	Sponsor/Country of study	Phase, (Patients), Severity	Results	References
Baricitinib and LPV/R		RT, OL, NoR	Ministero "Ricerca corrente"/IT	I (24) Moderate	Reduced symptoms and disease progression	42
Baricitinib and LPV/R	NCT04358614	OB, RT, LN, MC	Hospital de Prato/ IT	II (191) Moderate	Reduced symptoms, viral load, and disease progression	43
Baricitinib and corticosteroid	EUPAS34966	OB, PR, SC	U. General Hospital of Albacete/ES	(112) Moderate - severe	Improved pulmonary function and reduced the need for oxygen	41
Danoprevir and ritonavir	NCT04291729	IN, OG, OL /CM	The Ninth Hospital of Nanchang/CN	IV (11) Moderate	Suppressed viral replication in less than a week	53
HQ and oseltamivir	NCT04303299	IN, R, PR, PL	Rajavithi Hospital/ TH	III(320) Mild	At high doses, viral load decreased compared to the control	65
HQ and oseltamivir	NCT04349241 (-)	R, IN, OL, ST	Ain Shams University/ EG	III (100) Mild-moderate	Decreased viral load in 8 days	64
HQ, FVP, DRV, and ritonavir	NCT04303299	IN, R, PR, ST	Rajavithi Hospital/ TH	III(320) Moderate-severe	Together they had higher viral clearance	65
IV, AAS, DEX, and ENOX*	NCT04425863	OB,PS/ CM	Eurnekian Public Hospital/AR	167 Mild-severe	Reduced mortality and disease progression	78
LPV-R, IFNβ-1b, ribavirine	NCT04276688	IN, MC, PR, OL	The University of Hong Kong/ HK	II (127) Mild-moderate	Significantly reduced viral load	56
Novaferon and or LPV/R	ChiCTR2000029496	R, OL, PR, IN	The First Hospital of Changsha /CN	(89) Moderate-severe	Significantly reduced viral load	46
Remdesivir alone or with baricitinib	NCT04401579	IN, R, PR, DB, MC, PL/ CM	I. Allergy and Infectious Diseases/ US, DK, JP, KR, MX, SG, ES, GB	III (1033) Moderate-severe	Baricitinib with remdesivir reduced recovery time and improved clinical status	58

*Natural products or their semi-synthetic derivatives.
COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CM: completed; DB: double-blind; IN: interventional; LN: longitudinal; MC: multicenter; NoR: non-randomized; OB: observational; OG: one group; OL: open-label; PL: placebo; PR: parallel; PS: prospective; R: randomized; Rt: retrospective; SC: single center; ST: standard therapy. AR: Argentina; CN: China; DK: Denmark; EG: Egypt; ES: Spain; GB: United Kingdom; HK: Hong Kong; IT: Italy; JP: Japan; KR: South Korea; MX: Mexico; SG: Singapore; TH: Thailand; US: United States; ASA: Acetylsalicylic acid; DEX: Dexamethasone; DRV: Darunavir; ENOX: Enoxaparin; FVP: Favipiravir; HQ: Hydroxychloroquine; IFN: Interferon; IV: Ivermectin; LPV/R: Lopinavir with Ritonavir. (-): retracted article.

in type II pneumocytes and blocks chromatin condensation and fragmentation by caspases, thus preventing cell apoptosis (Fig. 2)[9]; it also blocks the release of IL-6 and TNFα[10]. When used in COVID-19, Aviptadil reduced respiratory failure and mortality by ~50% when patients were treated with the maximum standard of care in tertiary care hospitals but not in regional secondary care hospitals[10].

Anakinra (Kineret) is a recombinant form of the IL-1 receptor antagonist. It is a disease-modifying antirheumatic drug that inhibits nuclear factor-kappa B (NFκB) translocation (Fig. 2), thereby controlling the production of proinflammatory mediators[11]. It reduced the 30-day mortality by 50% and improved patients' ability to breathe. Pyridostigmine bromide (Mestinon) also

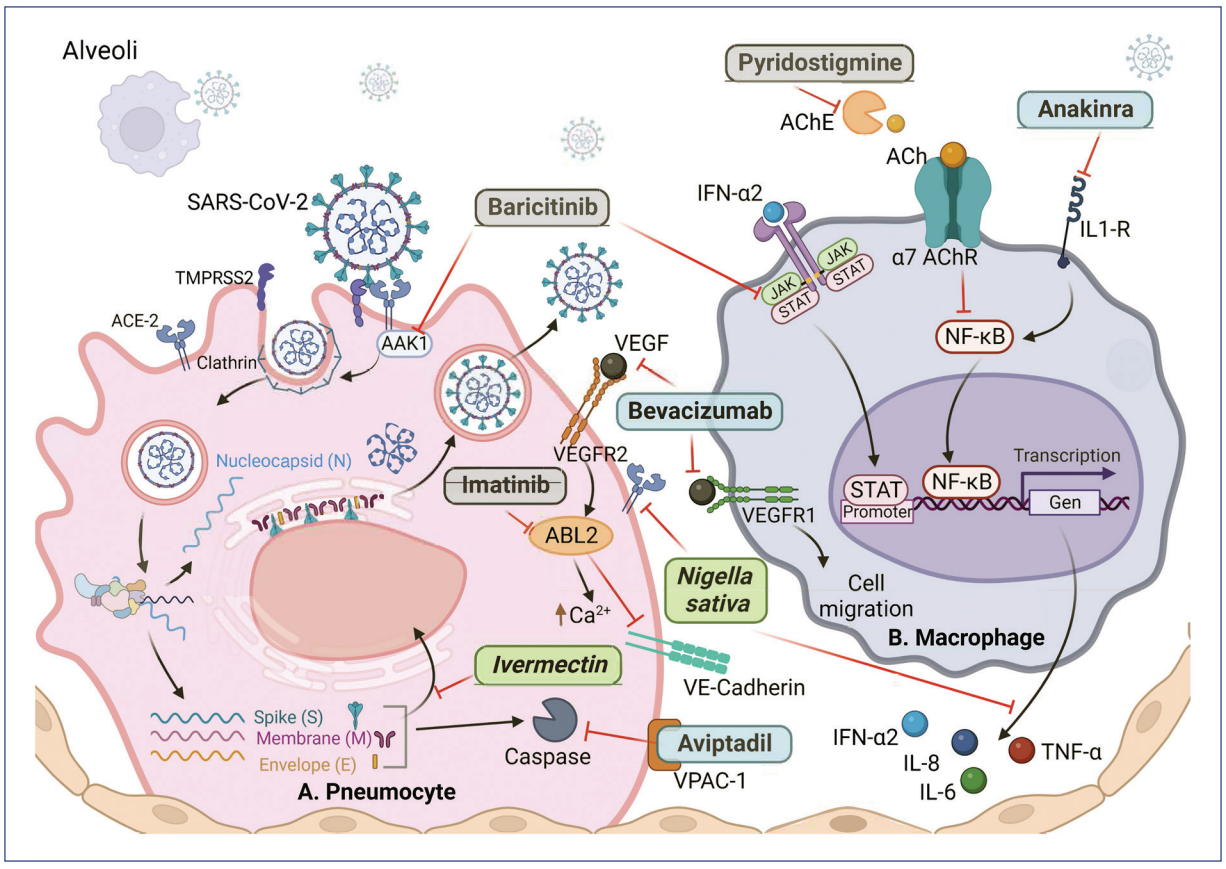

Figure 2. Drugs with greater potential against SARS-CoV-2 and COVID-19. **A:** type II pneumocyte. **B:** macrophage. ACE2: angiotensin 2 receptor; TMPRSS2: transmembrane serine protease 2; AAK1: AP2-associated protein kinase-1; VEGFR2/1: vascular endothelial growth factor receptor; ABL2: ABL tyrosine kinase; JAK: Janus kinase; STAT: signal transducer and activator of transcription; IFN-α2: interferon-alpha-2; AChE: acetylcholinesterase; ACh: acetylcholine; IL1-R: IL-1 receptor; NF-κB: nuclear factor enhancer of activated B-lymphocyte kappa light chains; VE-Cadherin: vascular endothelial cadherin. Natural products in green, biological in blue, synthetic in gray. Figure created on BioRender.com.

inhibits NFκB because it is an acetylcholinesterase inhibitor, and its activity results in an increase in the half-life of acetylcholine, which is critical in the cholinergic anti-inflammatory pathway[12-14] (Fig. 2); its administration reduced the need for mechanical ventilation by 2 days and reduced mortality by 63%[15].

Thalidomide is an anti-inflammatory, immunomodulatory, and anti-angiogenic drug that inhibits the NFκB and interferon regulatory factor 3 (IRF3) pathways[16]. Thalidomide, in combination with glucocorticoids, reduced hospital stay and viral load by ~50%, decreased IFN-γ and IL-6 levels, and the need for mechanical ventilation[17]. In addition, chloroquine, an antimalarial and arthritis drug, inhibits the inflammatory response mediated by IL-6, IL-17, and IL-22 and prevents viral entry by interacting with ACE2[18]. Chloroquine (400 mg, 2 times daily for 4 days) showed a mortality rate of 15% versus 39% in the high-dose group (600 mg, 2 times daily for 10 days)[19]. The mortality rate was similar to that of the thalidomide control group (16%), so its efficacy is questionable, and the use of high doses in critically ill patients is not recommended.

Fluvoxamine is an antidepressant that pharmacologically functions as a selective serotonin reuptake inhibitor. It inhibits the production of TNF-α and IL-6 through the S1R-IRE1 pathway[20]. Patients treated with fluvoxamine experienced no clinical worsening compared to 8.3% in the placebo group[21], while tocilizumab (Actemra), an IL-6 receptor inhibitor, induced recovery of patients requiring supplemental oxygen in a median of 4 days in tertiary care[22], compared to 10 days for patients treated with remdesivir[23]. However, several clinical trials have suggested that tocilizumab may not be effective against COVID-19[11,24,25] because, unlike the drugs above, which inhibit the upstream inflammatory response, tocilizumab only inhibits IL-6 activity.

Treatment with *N. sativa* (*Ranunculaceae*) seeds and honey was evaluated in a study conducted at a tertiary care center in Pakistan. It reduced the time to symptom relief by 50%, accelerated viral clearance, and reduced the mortality rate fivefold (4% vs. 18.8% for placebo)[26], while *N. sativa* seed oil increased the percentage of recovered patients (62%) compared to the control (36%) and reduced the recovery time in a study conducted at a tertiary care center in Saudi Arabia[27].

In both studies, most patients were under 60 years of age, while the average age in the Saudi Arabian group was 36 years. Both studies showed a significant benefit from using *N. sativa* seeds, resulting in remission of symptoms. There were differences in the baseline characteristics of the patients in terms of comorbidities, as the Pakistani group had a higher percentage of hypertension and obesity. In addition, various concomitant treatments were used due to the greater severity of the disease compared to the patients in the Saudi Arabian study, where the use of other medications was not reported (Table 4).

The main phytopharmaceutical of this seed is thymoquinone, which has anti-inflammatory effects by suppressing expression of enzymes that produce prostaglandins and leukotrienes and also blocks ACE2 (Fig. 2)[28]. This species also contains nigellone, which blocks histamine release[29]. The oil showed antiviral activity in a murine cytomegalovirus and H9N2 model and decreased proinflammatory cytokines in a murine allergic asthma model[28].

Antimitotics

Colchicine, an alkaloid derived from the plant *Colchicum autumnale* (*Colchicaceae*), used in the treatment of gout, inhibits tubulin polymerization in leukocytes and acts on the NLRP3 inflammasome[30]. Colchicine-reduced mortality and hospitalization by 24% compared with placebo in patients over 40 years of age with COVID-19 confirmed by polymerase chain reaction (PCR)[31].

Complement system inhibitors

Eculizumab (Soliris) is a monoclonal antibody used to treat autoimmune diseases; it is an inhibitor of complement protein C5b-9[32] and reduces the levels of IL-1, IL-6, and TNFα[33]. In one study, it contributed to the improvement of 6 out of 8 patients[32]. Ravulizumab (Ultomiris), on the other hand, is a complete inhibitor of C5 convertase, which is the initiator of the terminal phase of the complement system[34], so in addition to preventing complement-mediated inflammation, it also blocks cell activation and lysis[35].

Tyrosine kinase inhibitors

Imatinib mesylate, a c-ABL kinase inhibitor used to treat certain cancers, inhibits VE-cadherin dissociation (Fig. 2), preventing capillary leakage and alveolar edema; it also reduces IL-6 and IL-8 secretion[36]. Imatinib mesylate reduced the median duration of mechanical ventilation from 12 to 7 days and reduced the likelihood of death in patients by 49%[37].

Baricitinib (Olumiant), an inhibitor of Janus kinase (JAK) 1 and 2 kinases used in the treatment of rheumatoid arthritis, decreases the expression of ACE2 in human liver cells and the expression of proinflammatory cytokines induced by IFN-α2 through the JAK/signal transducer and activator of transcription (STAT) pathway[38,39]. In addition, it has affinity for the AP2-associated protein kinase-1 and reduces SARS-CoV-2 endocytosis (Fig. 2)[40]. Baricitinib reduced respiratory failure, mortality, and disease progression by 50%[38], and in another study where it was administered with corticosteroids, supplemental oxygen requirements were reduced (25.8% vs. 62% in the methylprednisolone control group), and mortality was ~4% in both groups[41], suggesting that corticosteroid activity reduced mortality. Baricitinib in combination with lopinavir and ritonavir (Kaletra) improved patient status and prevented disease progression[42], and in another study, inhibited mortality, reduced disease progression by 95% (0.88% vs. 17.9% control), and increased hospital discharge rate (9.7% vs. 1.3%)[43].

Tofacitinib as baricitinib, is an inhibitor of JAK1 and 3 kinases and the JAK/STAT pathway used to treat rheumatic diseases. Tofacitinib alone reduced mortality at day 28 by 49% (2.8% vs. 5.5% for placebo) and the cumulative incidence of death or respiratory failure by 37.6% (18% vs. 29% for placebo)[44]. Meanwhile, Novaferon, an antitumor/antiviral protein that interacts with the IFN2 receptor, a JAK/STAT45 signaling pathway[45], with or without lopinavir and ritonavir, had a higher viral clearance rate at day 6 than the lopinavir/ritonavir group (50.0% vs. 24.1% and 60.0% vs. 24.1%, respectively)[46].

Acalabrutinib improved lung function and reduced inflammation by targeting BTK tyrosine kinase; BTK is important in activating the innate immune response of blood monocytes[47] by promoting inflammasome and phagocytic receptor activation[48]. In addition, BTK inhibition also blocks nuclear translocation of NFκB, which results in a reduction of the synthesis of proinflammatory cytokines. Also, the activity of opaganib, which is an inhibitor of sphingosine kinase-2. This kinase has been proposed to be a factor in viral replication[49,50], and its inhibition also decreases TNF-α and IL-6. In patients, it

Table 4. Characteristics of clinical studies with individually administered drugs

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Acalabrutinib	NCT00001467; NCT01200953	100 mg PO, BID for 14 days or placebo	Steroids and/or hydroxychloroquine	Median age 61 years, 68% men, hypertension 84%, obesity 68%, and diabetes mellitus 37%	National Institutes of Health Clinical Center (CC). Tertiary	47
Anakinra* (Kineret)	NCT04357366	100 mg SC, QD, for 10 days or placebo	ND	Mean age 63 years, 62.3% men, diabetes 31.5%, hypertension 52.3%	13 centers, tertiary	11
Aviptadil (Zyesami)	NCT04311697	Aviptadil IV, 3 days in titrated doses of 50 pmol, 100 pmol, 150 pmol/kg/h or placebo	ND	62.6% younger than 65 years, 64.9% men	Five centers, secondary and tertiary	10
Baricitinib	NCT04393051	Italy: 4 mg/day for 14 days along with standard of care. Spain: 2 or 4 mg/day for 3-11 days or placebo	Hydroxychloroquine, antibiotics, protease inhibitors, enoxaparin, and steroids	Mean age 80 years, 65.2% men, 73.9% hypertension, 45.7% diabetes	Spain: Complejo Hospitalario Universitario de Albacete. Italy: University of Pisa. Tertiary	38
Bevacizumab*	NCT04275414	Single dose of 500 mg dissolved in 100 mL of saline solution, IV or placebo	Lombardy and Wuhan: antivirals, hydroxychloroquine, antibiotics, steroids, antipyretics, and supportive care. Wuhan: Chinese herbal medicine in all patients	Mean age 62 years, 77% men, 50% hypertension, and 23% diabetes	China: Renmin Hospital of Wuhan University, Wuhan, Hubei Province. Tertiary Italy: Hospital S.p.A. Ospedale Generale di Zona Moriggia Pelascini. Secondary	70
Pyridostigmine bromide	NCT04343963	60 mg/day PO, 14 days or until hospital discharge	Dexamethasone 74.5% and tocilizumab (5.3%)	Average age 52 years, 59.6% men, diabetes 36.2%, hypertension 35.1%, and obesity 43.1%	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Tertiary Instituto Nacional de Cardiología Ignacio Chávez (INCICh). Tertiary	15

(Continues)

Table 4. Characteristics of clinical studies with individually administered drugs *(continued)*

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Chloroquine	NCT04323527	High dose: 600mg BID for 10 days Low dose: 450 mg BID on day 1 and QD for 4 days	Ceftriaxone IV (1g 2 BID for 7 days), azithromycin (500 mg QD for 5 days), oseltamivir (75 mg BID for 5 days) in case of influenza	Mean age 51.1 years, 75.3% male, hypertension 45.5%, alcohol use disorder (27.5%), and diabetes (25.5%)	Hospital e Pronto Socorro Delphina Rinaldi Abdel Aziz. Tertiary	19
Colchicine†	NCT04322682	0.5 mg oral, twice a day for 3 days and then once a day for 27 days	Hydroxychloroquine (0.5%), oral anticoagulant (2.1%), aspirin (8.7%), other platelet agents (1.4%)	Mean age 54 years, 53.9% women. Hypertension (34.9%), respiratory disease (26.1%), diabetes (19.9%)	Eight centers. Secondary and tertiary	31
Eculizumab*	NCT04346797	900 mg every week, 900 mg every 4 days and 3 doses of 1,200 mg on days 1, 4 and 8 showed the most satisfactory results. Intravenous	Enoxaparin, unfractionated heparin, dexamethasone	Hypertension (87.5%), diabetes (37.5%)	Hôspital saintlouis aphp, ND	32
Favipiravir	CTRI/2020/05/025114	1800 mg twice daily 1; maintenance dose of 800 mg twice daily thereafter, maximum 14 days	Antipyretics, cough suppressants, antibiotics, and vitamins.	73.5% men, 77.6% aged 30 to 60 years, 25.9% with diabetes mellitus, hypertension and/ or obesity	AIIMS India. Tertiary. Breach Candy Hospital Trust Secondary. Dr. Balabhai Nanavati ND Hospital. Fortis Hospital Limited, primary to quaternary	61
Favipiravir versus umifenovir (Arbidol)	ChiCTR2000030254	1600 mg, twice on the first day followed by 600 mg, twice daily, for the next few days. Or Arbidol (200 mg, 3 times a day) plus standard care for 7 days	Traditional Chinese herbal medicines, antibiotics, additional antiviral treatment, immunomodulatory drugs, steroids, antipsychotic drugs, nutritional support, cardiovascular drugs, oxygen support, non-invasive positive pressure ventilation (NPPV), or invasive ventilation	In favipiravir group 50.86% men, 75% < 65 years, 31.05 hypertension, 12.07% diabetes. In Arbidol group 42.50% men, 65.83% < 65 years, 25% hypertension, 12.07% diabetes	Zhonghan Hospital of Wuhan University. Tertiary Leishenshan Hospital, field hospital Hospital of Hubei Province, Wuhan, Tertiary	62
Fluvoxamine	NCT04342663	50mg once, 100 mg 2 times a day for 2 days, then 100 mg 3 times	ND	Diabetes 11%, hypertension 19%, 30% male	BJC Belleville. Primary. Washington University	21

(Continues)

Table 4. Characteristics of clinical studies with individually administered drugs *(continued)*

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
		a day as tolerated until day 15			School of Medicine. Tertiary	
Nitric oxide gas	NCT04305457	NO inhaled at 160 ppm for 30 min, twice daily for 14 days or until discharge	ND	Hypertension 41%, diabetes 34.5%, 65.2% male	Massachusetts General Hospital. Tertiary	72
LMWH	NCT04323761	Subcutaneous enoxaparin 40-60 mg daily, or therapeutic 40-60 mg subcutaneously twice daily	Hydroxychloroquine LPV/r or DRV/r, doxycycline dexamethasone, prednisone, methylprednisolone, hydrocortisone), macrolides, baricitinib tocilizumab remdesivir	Hypertension 46.03%, 19.68% diabetes, 76.2% male, mean age 70 years old	University Hospital of Pisa, Italy. Tertiary	24
Imatinib mesylate	EudraCT 2020-001236-10	800 mg oral on day 0 followed by 400 mg daily on days 1-9	ND	Median age 64 years, diabetes 25%, cardiovascular disease 22%, hypertension 37.6%	VU University Medical Center. Tertiary Erasmus MC (Rotterdam). Tertiary, Spaarne Ziekenhuis (Haarlem). Secondary. Haaglanden Medical Center (the Hague) Secondary. Isala Clinic (Zwolle) Primary	37
Nigella Sativa oil‡	NCT04401202	500 mg of *Nigella sativa* oil in capsule, 2 times a day for 10 days	ND	Average age 36 years old, 36% male, 8% diabetes, and 9% hypertension	King Abdulaziz University Hospital. Tertiary	27
Nigella sativa and honey‡	NCT04347382	Honey 1 g/kg/ day and *Nigella sativa* seeds 80 mg/kg per day for 13 days	Panadol, azithromycin, montelukast, LMWH, hydrocortisone, multivitamins, tazobactam+ piperacillin, ivermectin, meropenem, at physician's consideration	56.86% men, 49.84% ≤ 40 years, hypertension 31.62%, and diabetes 36.74%.	Shaikh Zayed Post-Graduate Medical Complex, Services Institute of Medical Sciences, Doctor's Lounge, and Ali Clinic. Tertiary	26

(Continues)

Table 4. Characteristics of clinical studies with individually administered drugs *(continued)*

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Opaganib	NCT04414618	2 × 250 mg of oral Opaganib in capsules or placebo every 12 h for up to 14 days	Remdesivir and/or corticosteroids	Mean age 58 years, 64.3% male	Honor Health Research Institute, Miami Cancer Institute, Tertiary. Oregon Health & Science University, Albany Medical Center, Henry Ford Hospital, Ziv Medical Center, Tertiary	51
Ravulizumab*	NCT04369469	Day 1: 2400 mg, 2700 mg, or 3000 mg if they weighed ≥ 40- < 60 kg, 60- < 100 kg, or ≥ 100 kg, respectively. On days 5 and 10 600 mg if they weighed < 60 kg and 900 mg if they weighed ≥ 60 kg, then 900 mg on day 15	Antivirals such as remdesivir	54.5% men, mean age 66 years, diabetes 50%, hypertension 45.5%	Brigham and Women's Hospital Tertiary, Houston Methodist Hospital, Quaternary, King's College Hospital Tertiary, Washington University School of Medicine. Tertiary	34
Remdesivir	NCT04292730	Intravenous remdesivir 200 mg on day one, followed by 100 mg/day For 5-10 days or standard care	Steroids, hydroxychloroquine/ chloroquine, lopinavir-ritonavir, tocilizumab, azithromycin, aspartate aminotransferase, alanine aminotransferase	Average age 57 years old, 61.13 male, 42.46% hypertension, 39.72% diabetes	105 hospitals in the US, Europe, Asia: Secondary and tertiary	57
Remdesivir	NCT04280705	Intravenous 200 mg on day one and 100 mg daily for up to 9 additional days	Hydroxychloroquine and glucocorticoid	Average age 58.9 years, 64.4% men, 50.2% hypertension, 44.8% obesity, and 30.3% diabetes mellitus	60 centers ND	23
Thalidomide	NCT04273529	100 mg per day for ≥ 7 days, with a median duration of 12 days	Dexamethasone in low doses (40 mg IV every 12 h for 3 days, then every 24 h for 5 days)	66.7% male, median age 65.5 years 50% with comorbidities	First Affiliated Hospital of Wenzhou Medical University. Tertiary	17
Tocilizumab*	NCT04331795	Range of 40, 80, 120 and 200 mg, with possible repetition at 24 or 48 h	Hydroxychloroquine or azithromycin, lopinavir-ritonavir, or systemic corticosteroids	Median age 69 years, 50% men, 62% two or more comorbidities	University of Chicago Medicine. Tertiary	22

(Continues)

Table 4. Characteristics of clinical studies with individually administered drugs *(continued)*

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Tofacitinib	NCT04469114	10 mg oral or placebo 2 times daily for up to 14 days or until discharge	It may have included glucocorticoids, antibiotic agents, anticoagulants, and antiviral agents	Mean age 56 years, 65.1% men, 50.2% with hypertension, and 23.5% with diabetes	Multicenter, 17 locations, Secondary and Tertiary	44
Umifenovir (Arbidol)		2 pills 0.2 g 3 times daily	Interferon, asmeton (compound methoxyphenamine), limonene and pinene, moxifloxacin, ibuprofen, and ambroxol	54.8% men, 17.7% hypertension, 11.3% diabetes. Most between 48 and 63 years old	First Hospital of Jiaxin Tertiary	63
Vitamin D_3[†]	NCT04560608	Group 1: 50,000 IU per month, 80,000 IU or 100,000 IU every 2-3 months the year before infection. Group 2: 80,000 IU within a few hours of COVID-19 diagnosis	Antibiotics, corticosteroids, and pharmacological treatments for respiratory disorders	Mean age 88 years, 50.6% men. 63.6% hypertension, 54.5% cardiomyopathy	Angers University Hospital Tertiary	75

*Biologicals.
[†]Natural products or their semi-synthetic derivatives.
[‡]Herbal remedy.
SA: Saudi Arabia; BR: Brazil; CA: Canada; CH: Switzerland; CN: China; DE: Germany; ES: Spain; FR: France; GB: United Kingdom; GR: Greece; HK: Hong Kong; IN: India; IL: Israel; IT: Italy; JP: Japan; KR: South Korea; MX: Mexico; NL: Netherlands; PK: Pakistan; SE: Sweden; SG: Singapore; TW: Taiwan; US: United States; LMWH: low molecular weight heparin; IV: intravenous; PO: oral; SC: subcutaneous; QD: once daily; BID: twice daily; TID: three times daily; ND: Not described. NO: Nitric oxide.

reduced the need for supplemental oxygen (61.6% vs. 46.7% placebo) and accelerated hospital discharge[51].

Antivirals

Danoprevir is an inhibitor of hepatitis C virus NS3/4a protease, which has high structural similarity to Mpro of SARS-CoV-2[52], while ritonavir increases danoprevir exposure by inhibiting cytochrome P450 isoenzyme 34A. Danoprevir with ritonavir suppressed viral replication in < 1 week and reduced ground glass opacity[53].

Lopinavir and ritonavir are HIV-1 protease inhibitors; ribavirin inhibits normal viral replication, and IFN β-1b induces the synthesis of antiproliferative and immunomodulatory proteins[54]. Meanwhile, lopinavir and ritonavir had no clinical benefit when administered alone[24] or with Arbidol[55]. Treatment with lopinavir and ritonavir with ribavirin and IFN β-1b, administered 7 days after symptom onset, reduced the median time for negative nasopharyngeal swab results compared to the control group (from 12 to 7 days), suppressed viral load at 8 days, relieved symptoms at 4 days, and reduced IL-6 levels[56].

Remdesivir reduced the median recovery time by 10 days (vs. 15 days for placebo) and also reduced mortality (6.7% vs. 11.9% for placebo) in a study conducted in 60 tertiary care hospitals in Europe, Asia, and the Americas in patients with moderate to severe illness[23]. In another study conducted in 105 secondary and tertiary care hospitals in the U.S., Europe, and Asia in patients with moderate illness, 5 days of remdesivir improved the condition of patients compared to placebo. However, the clinical significance was uncertain due to the study design[57]. In another study conducted in 71 centers in eight countries in Europe, Asia, and the Americas, remdesivir was administered alone or in combination with baricitinib, and in the second case, the median recovery time was reduced from 8 to 7 days[58].

The protocols of the three studies were the same in terms of doses. However, there was a difference in the duration evaluated, as the first study found that the 10-day treatment was sufficient to shorten patients' recovery time. In contrast, the second study found that a 5-day treatment was more beneficial than a 10-day treatment. From these data, it can be concluded that a 10-day course provides greater benefit in patients with more advanced diseases (Tables 4 and 5).

We also found two articles that are not included in the results tables. In one, remdesivir was administered for 5 or 10 days and produced a clinical improvement of 2 points or more on the 7-point ordinal scale at day 14 in 64% of patients; however, they found no significant differences between the two groups, in patients with severe disease who did not require mechanical ventilation[59]. In another study in China with critically ill patients, remdesivir did not affect clinical improvement[60]. Therefore, the benefit of remdesivir is uncertain; it appears that its individual activity may not be sufficient to improve clinical status significantly.

Favipiravir is an influenza virus RNA polymerase inhibitor. It has been evaluated in various studies in patients with mild to severe disease in which it did not reduce viral load; it only showed a reduction in the recovery time of patients from 5 to 3 days in a study conducted in India[61] and in a study conducted in China it contributed to 71% of patients recovering before 7 days versus 55% in the group with umifenovir[62]. The latter study used lower doses, with a difference of 200 mg. Both studies were conducted in tertiary care hospitals, and the patients evaluated had similar characteristics in terms of disease status. However, the standard of care differed in that the Chinese study used herbal medicines and additional antiviral treatment. Both studies concluded that favipiravir therapy accelerated patient recovery but had no effect on viral load reduction (Table 4).

On the other hand, umifenovir, a broad-spectrum antiviral[61,63] that prevents the hemagglutinin from switching to its fusion state, thereby inhibiting the entry of the virus, also reduced the recovery time of symptoms such as fever (4.9 vs. 6 days) and dry cough (4.3 vs. 5 days)[63].

Oseltamivir inhibits influenza virus neuraminidases, limiting the spread of infection and inflammation. Patients who received hydroxychloroquine with oseltamivir had a negative reverse transcriptase-PCR (RT-PCR) test in an average of 8.1 days[64] (article retracted due to questionable results). In another study, patients had a negative RT-PCR test 4 days earlier than the control group (7.5 vs. 11.5 days)[65]. This is important because it reduces the period of infectiousness and the risk of disease progression.

Antithrombotics

Low-molecular-weight heparin is an anticoagulant that enhances antithrombin III activity, reduces the risk of coagulopathy and thromboembolism, and interacts with NF-κB by mediating the production of proinflammatory cytokines[66]. It reduced the likelihood of death by 64% and the risk of disease progression and death by 39%[24].

Chemotaxis inhibitors

It is possible that the effect of bevacizumab is related to the secretion of vascular endothelial growth factor (VEGF) by leukocytes in response to a hypoxic environment[67] and that inhibition of VEGF (Fig. 2) prevents its function as a chemoattractant for monocytes and macrophages through its receptor VEGF receptor 1[68]. Bevacizumab reduced fever in the first 72 h, improved respiration in populations from China and Italy, and no patients died. However, a decrease in respiratory capacity was observed only in the control group in Italy throughout the study[69]. This is probably due to the use of Chinese herbal medicine, including Jinhua Qinggan, Lianhua Qingwen, and Xuebijing[70], in the treatment of all control patients in Wuhan, unlike those in Italy[69] (Table 4 for more data on concomitant treatments).

Bronchodilators

Inhaled nitric oxide reduced respiratory rate, improved oxygenation, and prevented hospital readmissions after discharge[71]. In addition to its bronchodilator activity, it is thought to have antiviral activity, as it reduced viral replication by 99% in *in vitro* studies by inhibiting the Mpro protease of SARS-CoV-2[72].

Vitamins

Regular supplementation with Vitamin D_3 during the year before illness significantly reduced mortality; the clinical benefit was not significant in patients who received it after diagnosis[73]. In an extension of this trial, Vitamin D_3 supplementation before, during, or after hospitalization reduced mortality in geriatric patients[74]. Vitamin D regulates innate and adaptive immunity, as its hormonal metabolite (calcitriol) mainly suppresses the production of inflammatory cytokines, induces regulatory T lymphocytes, and has a possible antiviral effect[75].

Table 5. Characteristics of clinical studies of combination therapies

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Baricitinib and LPV/R		Baricitinib 4 mg QD, PO for 14 days. LPV/R 250 mg, PO, BID, 14 days	Hydroxychloroquine 400 mg/QD/PO, LPV/R	83% men, mean age 63.5 years, 20.83% hypertension, 29.16% diabetes	Hospitals in Prato and Alessandria. ND	42
Baricitinib and LPV/R	NCT04358614.	Baricitnib 4 mg, PO, QD, 14 days. LPV/R 250 mg PO BID, 14 days	HQ, LPV/R	62.30% men, mean age 65.5 years, 27.74% hypertension, 16.23% diabetes	7 care centers, ND	43
Baricitinib and corticosteroid	EUPAS34966	Baricitinib 4 mg PO the 1st day, then 2 mg QD or 4 mg QD Methylprednisolone 80, 125 or 250 mg/QD	LPV/R, two tablets PO 200/50 mg BID, 7-10 days HQ 200 mg, PO, BID	Mean age 63 years, 69.6% men, 28.8% hypertension, 18.8% diabetes	Hospital General Universitario de Albacete, Spain, Tertiary	41
Danoprevir and ritonavir	NCT04291729	Danoprevir 100 mg PO, BID, 4-12 days, Ritonavir 100 mg PO, BID	α-interferon, 5 million units, IN BID	Mean age 44 years, 36.4% men, 18.2% hypertension	The Ninth Hospital of Nanchang Tertiary	53
HQ and oseltamivir	NCT04303299	Oseltamivir 300 mg/ QD O 4-6 mg/kg QD; HQ 800 mg QD	Supportive care without experimental treatments	Mean age 32 years, 46.6% male, 6.6% obese	Rajavithi Hospital Tertiary	65
HQ and oseltamivir	NCT04349241 (-)	Oseltamivir PO 75 mg BID 10 days; HQ 800 mg PO day 1, followed by 200 mg BID, days 2-10	ND	Mean age 36.4 years, 50% male, 18% with comorbidities ND	Ain Shams University Hospital, Tertiary y Assiut University Hospital, Tertiary	64
HQ, FVP, DRV yand ritonavir	NCT04303299	HQ 400 mg QD; FVP 6000 mg 1st day, then 2400 mg QD; DRV 1200 mg, QD or 4-6 mg/kg, QD; R 200 mg, QD or 2.5 mg/kg QD	Supportive care with no experimental treatments	Mean age 42 years, 52% men, 30% obese	Rajavithi Hospital Tertiary	65
IVE, AAS, DEX and ENOX*	NCT04425863	IVE PO 24, 36 and 48 mg days 0 and 7; DEX 4 mg IM; ENOX SC; ASA 250 mg PO	ND	Average age 55.7 years, 51.5% men	Hospital Eurnekian Secondary	78
LPV-R, IFNβ-1b, Ribavirine	NCT04276688	LPV 400 mg; R 100 mg BID, 14 days; ribavirin 400 mg BID; IFNβ-1b 8 million IU, TID every other day	Amoxicillin, azithromycin, ceftriaxone, doxycycline, levofloxacin, corticosteroids	Average age 52 years old, 54% men, 13% diabetes, 27% hypertension	6 centers	56
Novaferon and/or LPV/R	ChiCTR2000029496	Novaferon 40 µg TID, IN. LPV/R 200 mg/50 mg PO TID	ND	Average age 46, 50, 37 years in the different groups, 9% diabetes, 10% hypertension	First Hospital of Changsha city, ND	46

(Continues)

Table 5. Characteristics of clinical studies of combination therapies *(continued)*

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Remdesivir alone or with baricitinib	NCT04401579	Remdesivir 200 mg IV day 1, 100 mg day 2-10. Baricitinib 2mg BID 14 days	Standard support with no experimental drugs	Mean age 55 years, 63.1% male, 57% 2 or more coexisting conditions	71 centers	58

*Natural products or their semi-synthetic derivatives.
ASA: Acetylsalicylic acid; DEX: Dexamethasone; DRV: Darunavir; ENOX: Enoxaparin; FVP: Favipiravir; HQ: Hydroxychloroquine; IFN: Interferon; IVE: Ivermectin; LPV/R: Lopinavir with Ritonavir; PO: oral; IV: intravenous; SC: subcutaneous; IN: intranasal; IM: intramuscular; QD: once daily; BID: twice daily; TID: three times daily; ND: not determined; (-): retracted article.

Multi-target combination therapies

The combination of hydroxychloroquine with favipiravir, darunavir, and ritonavir reduced mortality by 25% compared with patients receiving oseltamivir, lopinavir, and ritonavir (4% vs. 16%)[65]. The individual effect of the drugs in this regimen against COVID-19 is inconclusive. However, he efficacy of this regimen is related to the inhibition of different stages of the viral cycle, as it includes antiviral agents, protease inhibitors, polymerase inhibitors, and an antiparasitic agent that may interfere with viral entry.

The combination of ivermectin, dexamethasone, acetylsalicylic acid (aspirin), and enoxaparin covers different aspects of the disease, as ivermectin blocks the IMPα/β1 import heterodimer on which nuclear trafficking of RNA virus proteins depends (Fig. 2)[76]. Aspirin is an antithrombotic agent in mild cases, enoxaparin is an anticoagulant[77], and dexamethasone inhibits transcription factors such as AP-1, NF-κB, and IRF[78], prevents the synthesis of cytokines and chemokines, and induces apoptosis of T lymphocytes and neutrophils[79]. This therapy inhibited disease progression and reduced mortality by 71% compared to the mortality rate in Argentina and 87% compared to the mortality rate in Spain and Italy for hospitalized patients[77].

Fig. 3 shows the molecular structure of the drugs included in clinical trials that were shown to inhibit the processes involved in SARS-CoV-2 infection.

Discussion

The global pharmaceutical industry has relied on developing prophylactic vaccines to reduce transmission through large-scale mass vaccination programs worldwide, aiming to achieve herd protection in the short term. Although highly effective vaccines have been developed, there is still significant mortality, as well as limitations in vaccine availability and the emergence of SARS-CoV-2 variants.

Drug repurposing is an alternative to the traditional drug development and discovery process to address emerging diseases such as COVID-19. In this study, we identified drugs, an herbal remedy, and a vitamin that were administered orally (23), intravenously (6), subcutaneously (3), intramuscularly (2), and inhalational (2). Twenty-four of these were administered alone, and 12 were in combination therapies that were shown to be effective against COVID-19 during the 1st year of the pandemic. Several of these drugs were recommended by the Instituto Mexicano del Seguro Social (Mexican Social Security Institute) for their use in patients with COVID-19 in the Clinical guide for the treatment of COVID-19 in Mexico (Guía clínica para el tratamiento de la COVID-19 en México).

The drugs that showed the best results in reducing mortality and the need for mechanical ventilation in critically ill, very severe and severe patients were those that reduced inflammation even though they were not specifically anti-inflammatory, such as the kinase inhibitors imatinib mesylate and baricitinib, the proinflammatory cytokine regulators aviptadil, anakinra, and pyridostigmine bromide, the monoclonal antibody bevacizumab, the herbal remedy based on *N. sativa* seeds with honey, and the combination of ivermectin, aspirin, dexamethasone, and enoxaparin; also, hydroxychloroquine in combination with favipiravir, darunavir, and ritonavir; and the anticoagulant low-molecular-weight heparin.

In mild-to-moderate cases, the drugs that reduced viral load, mortality, or prevented progression to severe disease were synthetic antivirals such as danoprevir with ritonavir, the combination of lopinavir with ritonavir, IFN β-1b and ribavirin, also umifenovir, favipiravir, the recombinant IFN novaferon, the kinase inhibitor

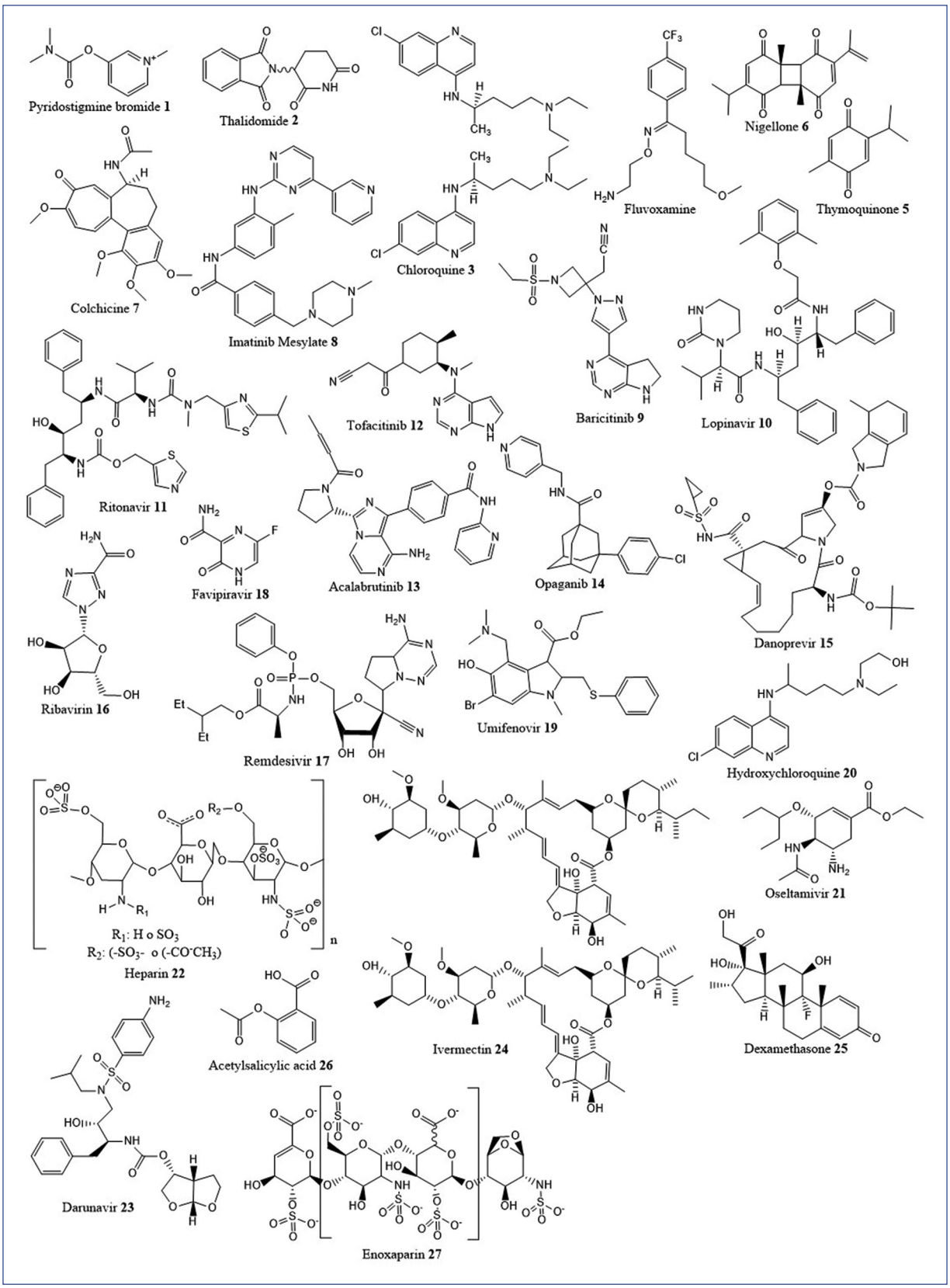

Figure 3. Molecular structure of drugs included in clinical studies that were shown to inhibit the processes implicated in SARS-CoV-2 infection.

tofacitinib, the natural product colchicine, and the semi-synthetic derivative hydroxychloroquine in combination with the antiviral oseltamivir.

We highlight the remarkable responsiveness of the drug repurposing strategy, which allowed clinical trials to be conducted early in the pandemic, reducing mortality, and recovery time; however, it is essential to continue to dedicate efforts to research and development of effective drugs and vaccines to have better, affordable, and easily accessible therapeutic options to face this pandemic and increase preparedness for future epidemics fully.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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