

REVIEW ARTICLE

Mast cells and histamine receptor-targeted adjunctive treatments for COVID-19: A literature review

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Abstract

With the rollout of multiple COVID-19 vaccines, adjunctive treatments for COVID-19 have received less attention. Breakthrough infections post-vaccination (including boosters) underscore the need to continue evaluating repurposed drugs and nutraceuticals as candidate adjunctive treatments. Early clinical studies of antihistamines hypothesized that targeting mast cells (and/or histamine receptors) might benefit COVID-19 patients. In cultured human coronary artery endothelial cells, histamine potentiated spike-mediated angiotensin-converting enzyme 2 internalization; this effect can be blocked by the antihistamine famotidine. This literature review focuses on clinical studies of antihistamines, mast cell stabilizers, and leukotriene receptor antagonists for COVID-19 patients. Several antihistamines and mast cell-targeting agents, including fluvoxamine, cyproheptadine, hydroxyzine, and antihistamines used alone or with azithromycin (dexchlorpheniramine, cetirizine, loratadine, and ebastine), as well as azelastine, famotidine (standard or high-dose), high-dose famotidine with celecoxib, and the flavonoid mast cell stabilizer quercetin, have been reported to be associated with clinical benefits in COVID-19 patients. Multiple studies have reported mixed results for aspirin, montelukast, and normal-dose famotidine; patients taking aspirin often have associated COVID-19 risk factors. In the context of current standard-of-care treatments, clinical studies evaluating candidate adjunctive treatments should carefully consider and avoid known drug–drug interactions, such as those involving celecoxib and dexamethasone. Further clinical studies of the identified treatments targeting mast cells and/or histamine receptors in COVID-19 patients associated with clinical benefits are therefore strongly recommended.

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Received: October 27, 2025**Revised:** November 20, 2025**Accepted:** December 8, 2025**Published online:** February 4, 2026**Copyright:** © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.**Publisher's Note:** AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.**Keywords:** COVID-19; Severe acute respiratory syndrome coronavirus 2; Mast cells; Antihistamines; Famotidine; Quercetin

1. Introduction

In March 2020, a team of volunteers found that high-dose famotidine provided some relief of COVID-19 symptoms in patients;¹ at the same time, lower standard doses of famotidine provided little or no relief.¹ Famotidine (Pepcid) is a histamine 2 (H₂) receptor antagonist medication used to reduce stomach acid production by antagonizing H₂ receptors expressed on mast cells, basophils, other immune cells,

and platelets.¹⁻⁴ (activated platelets release histamine and other inflammatory molecules). This mechanism raises the following question: Does targeting mast cells and basophils with other repurposed drugs show evidence of clinical benefits in COVID-19 patients? In addition, the histamine receptor H1 serves as an alternative receptor for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike protein and synergistically enhances viral entry by interacting with the human angiotensin-converting enzyme 2 (ACE2) receptor.⁵ In mice and rhesus macaques, mast cell degranulation induces alveolar epithelial inflammation and lung injury.⁶ Hafezi *et al.*⁷ present evidence that a cytokine response from mast cells may initiate inappropriate antiviral immune responses and cause the development of cytokine storm syndrome. In mice, mast cell degranulation in response to SARS-CoV-2 infection induced hyperinflammation and subsequent tissue lesions.⁸ Thus, this study provides a review of published clinical studies on drugs and nutraceuticals targeting H1 and H2 histamine receptors, mast cell stabilizers, and leukotriene receptor antagonists.

COVID-19 is caused by the SARS-CoV-2 virus. Clinical COVID-19 expression varies widely from asymptomatic to severe,^{9,10} including acute respiratory distress syndrome, cytokine storm, myocarditis, and pericarditis,^{11,12} and acute kidney injury. SARS-CoV-2 infections are also associated with multisystem inflammatory syndromes (MIS) in children, adults, and neonates, as well as post-acute sequelae of COVID-19 (also known as long COVID). Some cases of MIS may be associated with persistent SARS-CoV-2 infections.^{4,13-16} The SARS-CoV-2 Spike protein binds to the ACE2 receptor as a primary mechanism for infecting cells. A model for early COVID-19 cardiac pathology proposes that elevated histamine signaling through pericyte histamine receptors, and/or direct SARS-CoV-2 infections of pericytes, constricts cardiac pericytes and triggers capillary vasoconstrictions as the trigger event for COVID-19 cardiac pathologies.² This model also applies to COVID-19 vaccine-associated myocarditis and pericarditis.¹⁷ Hyperactivated mast cells, platelets, and constricted pericyte cells are also predicted to be the key cause of Kawasaki disease, MIS in children, adults, neonates, and post-COVID-19 vaccination.^{3,4,18} High-dose aspirin (acetylsalicylic acid), a non-steroidal anti-inflammatory drug (NSAID), is the standard treatment for both Kawasaki disease and MIS. Although Kawasaki disease and MIS are generally considered distinct, it has been proposed that MIS represents a SARS-CoV-2-associated form of Kawasaki disease, with disease onset triggered by hyperactivation of mast cells and histamine release from platelets.⁴ The induced pericyte constriction model may

also extend to kidney pericytes in acute kidney injury associated with COVID-19.

Clinical studies of several repurposed drugs and nutraceuticals support the hypothesis that targeting mast cells may benefit COVID-19 patients. These include multiple antihistamines, such as azelastine, cetirizine alone or with famotidine, high-dose famotidine alone or with celecoxib, chlorpheniramine, cyproheptadine with fluvoxamine, diphenhydramine, hydroxyzine, loratadine, and dexchlorpheniramine/cetirizine/loratadine/ebastine combined with azithromycin, as well as flavonoids quercetin and luteolin (associated with persistent COVID-19 olfactory dysfunction). Conflicting clinical studies were identified for aspirin, montelukast, and normal dosage famotidine.

2. Methods

2.1. Literature searches

A literature search was conducted on PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) using the terms “COVID-19” [Title/Abstract] AND “<treatment>”[Title/Abstract] for each of the following candidate treatments:

- (i) First-generation antihistamines: Antazoline, bepotastine, brompheniramine, carbinoxamine maleate, chlorpheniramine, cinnarizine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, hydroxyzine, meclizine, pheniramine, promethazine, and triprolidine
- (ii) Second-generation antihistamines: Astemizole, azelastine, bilastine, cetirizine, ebastine, emedastine, ketotifen, loratadine, mizolastine, olopatadine, rupatadine, and terfenadine;
- (iii) Third-generation antihistamines: Desloratadine, fexofenadine, and levocetirizine
- (iv) H2 receptor: Cimetidine, famotidine, nizatidine, and ranitidine
- (v) Mast cell stabilizers: Cromoglicic acid, cromolyn sodium, dasatinib, ketotifen, lodoxamide, luteolin, midostaurin, nedocromil, nilotinib, pemirolast, quercetin, and spaglumic acid
- (vi) Leukotriene receptor antagonists: Ibudilast, montelukast, pranlukast, verlukast, zafirlukast, and zileuton
- (vii) NSAID: Aspirin.

The Directory of Open Access Journals (DOAJ) (<https://doaj.org/>) was also searched for these same candidate treatments using the query “COVID-19 and <treatment>”. Candidate titles were reviewed manually to

select articles for this review. The Europe PMC database (<https://europepmc.org/>) was searched for “COVID-19 and <treatment>”; results were filtered by the <treatment> name in the article title. Exclusion criteria were: No patient data, non-English language, study protocols, non-human or non-COVID-19 studies (long COVID, MIS, Kawasaki disease), non-open access articles, and *in silico*/docking/bioinformatics/systems biology studies.

3. Results

The PubMed search returned 1,321 records (including duplicates). After title screening, 266 articles underwent full-text review. The highest number of records were retrieved for aspirin, famotidine, montelukast, quercetin, and luteolin. Ultimately, 98 articles (including a few supportive studies) were included, with an emphasis on candidate adjunctive treatments in COVID-19 patients. The DOAJ literature search identified 556 candidate titles, including duplicate titles. Of these 556 candidate titles, 41 additional new articles (not included in PubMed results) were identified for manual review, among which 16 articles were selected for inclusion. The Europe PMC search returned 22,487 titles excluding aspirin (only search results from PubMed and DOAJ for aspirin have been included in this review), and 34,600 titles, including articles and preprints for all target treatments. Of these 22,487 Europe PMC titles, 14 articles that did not overlap with previously selected articles from PubMed and DOAJ were selected. No relevant COVID-19 clinical literature was identified for antazoline, bepotastine, bilastine, carbinoxamine maleate, cromoglicic acid, dexbrompheniramine, dimenhydrinate, doxylamine, emedastine, lodoxamide, meclizine, midostaurin, mizolastine, nedocromil, olopatadine, pemirolast, pheniramine, pranlukast, rupatadine, spaglumic acid, terfenadine, triprolidine, and verlukast. Literature search results by treatment are summarized in Table A1.

3.1. Antihistamines

3.1.1. Azelastine

In a study of 90 patients, divided into two azelastine groups and one placebo group, negative COVID-19 polymerase chain reaction results occurred earlier and more frequently in the azelastine groups (18.52% and 21.43%) than in the placebo group (0%) by day 8.¹⁹ A study of 251 COVID-19 outpatients found that azelastine was associated with a significantly reduced viral load.²⁰ A clinical trial of 450 individuals found that azelastine was associated with a lower risk of SARS-CoV-2 infection (odds ratio [OR]: 0.31; 95% confidence interval [CI]: 0.11–0.87).²¹

3.1.2. Cetirizine

Dual-histamine receptor blockade with cetirizine and famotidine reduced pulmonary symptoms in COVID-19 patients.²² Cetirizine, used in combination with azithromycin in elderly patients suspected of COVID-19, was associated with no hospitalizations or deaths.²³ Cetirizine has also been shown to protect against myocarditis in a viral myocarditis mouse model.²⁴

3.1.3. Famotidine

Ad hoc dosage evaluations suggested COVID-19 symptom relief at higher famotidine dosages (80 mg three/four times a day) but not at standard heartburn dosages;¹ pharmacokinetic analyses of dosage levels were consistent with these *ad hoc* results.¹ The literature evaluating lower (normal) famotidine dose levels was fairly consistent with these early observations, reporting benefits^{25–31} and no benefits.^{32–42} High-dose famotidine has been reported to benefit COVID-19 patients.^{1,43–45} In a small randomized clinical trial of COVID-19 hospitalized patients ($n=20$), high-dose famotidine was associated with significant decreases in lactate dehydrogenase ($p=0.01$), mean white blood cell count ($p=0.04$), and length of hospital stay ($p=0.04$), along with a significant increase in oxygen saturation ($p=0.01$) and cough improvement ($p=0.02$).⁴⁵ A review of five studies found that famotidine was associated with a significant reduction in mortality (hazard ratio: 0.42; 95% CI: 0.21–0.85; $p=0.02$).⁴⁶ In cultured human coronary artery endothelial cells, histamine potentiated spike-mediated ACE2 internalization;⁴⁷ this effect can be blocked by famotidine.⁴⁷ In SARS-CoV-2-infected human colon carcinoma Caco2 cells, famotidine treatment inhibited histamine-induced toll-like receptor 3 expression and reduced toll-like receptor 3-dependent inflammatory signaling.⁴⁸ Combining high-dose famotidine with celecoxib exhibited positive results in COVID-19 patients;^{49,50} celecoxib is a cyclooxygenase-2 NSAID. High-dose famotidine and celecoxib treatment was associated with significant improvements in clinical, biomarker, and renal function measurements, including a reduction in the number, size, and shape of lung ground-glass lesions in all treated patients.⁵⁰ Theoharides and Conti⁵¹ raised concerns about treating COVID-19 patients with dexamethasone, a potent corticosteroid (steroidal anti-inflammatory drug). A retrospective study observed no deaths among 18 patients (0% mortality) receiving high-dose famotidine plus celecoxib, compared with six deaths among 21 patients (29% mortality) who also received dexamethasone ($\chi^2[1, N=43]=7.305$, $p<0.007$).⁵² Combining dexamethasone and celecoxib

significantly increased the risk of serious gastrointestinal problems, including bleeding, inflammation, ulceration, and potentially fatal perforation.⁵³ Despite reports of potential drug–drug interactions between celecoxib and dexamethasone,^{52–54} the NCT04488081 trial evaluated dexamethasone in combination with famotidine and celecoxib and was terminated early because of safety concerns.⁵⁵ In addition, aspirin combined with famotidine exhibited a significant synergistic survival benefit.⁵⁶

3.1.4. Additional antihistamines

Four patients with mild symptomatic COVID-19 who were treated with chlorpheniramine maleate nasal spray showed rapid improvement of their clinical symptoms.⁵⁷ Clinical trials NCT05449405/NCT05520944 compared 61 COVID-19 patients treated with chlorpheniramine maleate nasal spray to 40 placebo-treated patients and found an improved rate of clinical recovery ($p<0.05$) in the treated patients.⁵⁸ In the clinical trial NCT05087381, 147 COVID-19 patients treated with fluvoxamine and cyproheptadine showed no clinical deterioration compared to the majority who received standard-of-care treatment ($p<0.001$).⁵⁹ In an open-label, randomized clinical trial of 40 patients, cyproheptadine did not increase the number of ventilator-free days over 28 days.⁶⁰ In a multicenter observational study, the use of hydroxyzine among 164 COVID-19 patients within the first 48 h of hospitalization was associated with reduced mortality (adjusted OR: 0.51; 95% CI, 0.29–0.88; $p=0.016$).⁶¹ Treatment of 84 elderly (mean age 85) with suspected COVID-19 for 1 month with an antihistamine (dexchlorpheniramine, cetirizine, loratadine, or ebastine) combined with azithromycin for three to six days showed no association with hospitalizations or deaths.²³ A follow-up study of 468 COVID-19 patients reported a total of 20 (4.3%; OR: 0.490; 95% CI: 0.313–0.767; $p=0.001$) hospitalizations and three deaths (0.6%);⁶² none of the 468 COVID-19 patients treated with antihistamines developed long COVID-19.⁶² In K18-hACE2 transgenic mice, those treated with dasatinib and quercetin had a lower rate of meeting end-point criteria for euthanasia than the control group (30.7% vs. 64.7%).⁶³ In humanized mice infected with SARS-CoV-2, mast cell degranulation caused tracheal lesions and papillary hyperplasia; ebastine or loratadine effectively suppressed the induction of inflammatory factors in bronchial epithelial cells.⁸ In mice, remdesivir and loratadine reduced viral replication and inflammation.⁶⁴ In a retrospective case–control study of 3,712 COVID-19 patients, loratadine (OR: 0.20; 95% CI: 0.02–0.93) was identified among 11 drugs in reducing mortality.⁶⁵ In patients with moderate COVID-19 pneumonia, zafirlukast did not significantly improve symptom resolution.⁶⁶ In individuals over age

61, prior usage of loratadine ($n=284$; OR: 1.52; 95% CI: 1.12–2.07; $p=0.008$), cetirizine ($n=237$; OR: 2.09; 95% CI: 1.49–2.93; $p<0.001$), hydroxyzine ($n=269$; OR: 1.58; 95% CI: 1.11–2.25; $p=0.011$), diphenhydramine ($n=741$; OR: 1.55; 95% CI: 1.26–1.91, $p<0.001$), and azelastine ($n=135$; OR: 2.43; 95% CI: 1.47–4.02; $p=0.001$) was associated with a lower likelihood of SARS-CoV-2 positivity.⁶⁷ A retrospective survey of 13 COVID-19 patients who received chlorpheniramine either preventively or post-exposure reported favorable responses.⁶⁸ Diphenhydramine and lactoferrin improved survival rates in mice infected with SARS-CoV-2 compared to placebo-treated animals.⁶⁹ One intensive care unit (ICU) in India included a daily dosage of 5 mg of either desloratadine or levocetirizine in the treatment protocol for COVID-19.⁷⁰ A consecutive case series treated 53 COVID-19 patients (34 mild, 17 moderate, and 2 severe) with levocetirizine and montelukast, with no intubations or deaths (comparative mortality rates ranged from 1 to 7.5%).⁷¹ In a retrospective study of 59,094 patients, the risk of SARS-CoV-2 infection was significantly lower in H2 receptor antagonists (ranitidine: 50.27%; famotidine: 40.14%; cimetidine: 34.85%; and nizatidine: 10.35%) (OR: 0.85; 95% CI: 0.74–0.98; $p=0.024$).⁷² A propensity score-matched study of 9,469 participants found no association between use of H2 receptor antagonists and SARS-CoV-2 infection.⁷³ In addition, a clinical trial (NCT05504057) found reduced hospitalization and mortality rates among patients on antihistamines.⁷⁴ Furthermore, some COVID-19 patients were treated with antihistamines (e.g., bilastine⁷⁵) for symptoms, including skin lesions, rashes, urticaria (hives),⁷⁶ and cough, as well as for acute viral pharyngitis.⁷⁷

3.2. Mast cell stabilizers

3.2.1. Luteolin

Luteolin is a natural plant pigment-derived flavonoid and mast cell stabilizer known for its anti-inflammatory and antioxidant properties. It was found to bind to the Spike protein of SARS-CoV.⁷⁸ Luteolin exhibited anti-inflammatory properties in spike S1-induced THP-1 cell activation in a dose-dependent manner ($p<0.05$).⁷⁹ In a randomized trial, co-ultramicrosized palmitoylethanolamide with luteolin showed subclinical improvement with persistent COVID-19 olfactory dysfunction.^{80–82} Luteolin-7-O-glucoside inhibited replication of human coronavirus OC43 (a surrogate virus for SARS-CoV-2).⁸³ A clinical study of 42 COVID-19 outpatients showed reduced symptom severity, shortening time to testing negative.⁸⁴

3.2.2. Quercetin

Quercetin, a plant pigment-derived flavonoid, serves as a mast cell stabilizer. It is also a flavonoid found in many

plants and used in traditional Chinese medicine. A pilot study on the prevention of symptomatic COVID-19 in healthcare workers found that 1 of 60 in the quercetin group, compared with 4 of 60 in the control group, contracted COVID-19, indicating that quercetin may be a beneficial prophylactic treatment.⁸⁵ In the clinical trial NCT04377789 involving 113 healthcare workers, 1 of 71 in the quercetin group developed COVID-19, compared with 9 of 41 in the control group.⁸⁶ Evaluating quercetin for the prevention of symptomatic COVID-19 showed promise in a 3-month pilot study of 120 subjects.⁸⁵ A study of 60 patients with COVID-19 and concomitant type 2 diabetes mellitus treated with quercetin demonstrated reduced endothelial dysfunction and prevented thrombotic complications.⁸⁷ In the clinical trial NCT04861298 involving 100 COVID-19 outpatients with mild-to-moderate symptoms, the quercetin-treated group showed rapid recovery ($p=0.0004$) and improved resolution of acute symptoms ($p=0.0051$).⁸⁸ The clinical trial NCT04578158 of 152 COVID-19 outpatients found reductions in the frequency and length of hospitalization, the need for non-invasive oxygen therapy, and progression to ICUs (0 vs. 8), and reduced deaths (0 vs. 3).⁸⁹ In the NCT04603690 trial of 50 mild-to-moderate COVID-19 outpatients, the curcumin and quercetin-treated group showed faster viral clearance (72.0% in the treated group vs. 24.0% in the standard-of-care [SOC] control group).⁹⁰ In a trial of 50 patients with mild-to-moderate symptomatic COVID-19, 25 patients were treated with curcumin, quercetin, and Vitamin D3 (cholecalciferol), who showed expedited negative SARS-CoV-2 test results ($p=0.009$) and rapid resolution of acute symptoms.⁹¹ Treatment of 429 COVID-19 patients with at least one chronic disease and moderate-to-severe respiratory symptoms showed that those treated with quercetin, Vitamin C, and bromelain had a positive effect on laboratory markers of recovery.⁹² In mice, quercetin blocked the binding of the SARS-CoV-2 N protein to SMAD3, inhibiting acute kidney injury.⁹³ In a systematic review and meta-analysis of five studies with 544 patients, quercetin decreased the risk of hospital admission by 70% (relative risk [RR]: 0.30; 95% CI: 0.14–0.62), ICU admission by 73% (RR: 0.27; 95% CI: 0.09–0.78), and mortality by 82% (RR: 0.18; 95% CI: 0.03–0.98).⁹⁴ In a clinical trial of 60 patients with severe COVID-19, quercetin was significantly associated with earlier partial discharge and reduced serum levels of alkaline phosphatase, quantitative C-reactive protein (q-CRP), and lactate dehydrogenase.⁹⁵ Quercetin inhibited SARS-CoV-2 infection of green monkey kidney Vero E6 and human colon carcinoma Caco-2 cells in a concentration-dependent manner.⁹⁶ In an open-label clinical trial of 60 outpatients with mild-to-moderate COVID-19 pneumonia, the cranberry

(1,000 mg capsule for seven days) treatment group had lower CRP ($p=0.027$), D-dimer ($p=0.0001$), and ferritin ($p=0.002$) levels than the standard therapy group,⁹⁷ as cranberries contain compounds, including quercetin, flavanols, and proanthocyanidins.

3.3. Leukotriene receptor antagonists

3.3.1. Montelukast

Montelukast is a leukotriene receptor antagonist. In the clinical trial NCT04885530, montelukast did not reduce the duration of COVID-19 symptoms in 628 mild-to-moderate COVID-19 outpatients compared with 622 patients receiving a placebo.⁹⁸ In contrast, a retrospective study found that patients receiving montelukast experienced significantly fewer events of clinical deterioration ($p=0.022$).⁹⁹ A small randomized clinical trial of 67 patients with moderate-to-severe COVID-19 pneumonia reported significantly lower CRP ($p=0.042$) and D-dimer ($p=0.008$) levels in the montelukast-treated group compared to the control group.¹⁰⁰ In a double-blind clinical trial of 40 hospitalized COVID-19 patients, the montelukast-treated group showed significant improvements in CRP, LDH, and lymphocyte count ($p<0.05$).¹⁰¹ A multicenter, open-label, randomized controlled trial found montelukast therapy equally effective as inhaled steroids for the treatment of COVID-19 wheezing.¹⁰² Montelukast combined with gabapentin improved cough frequency and severity in hospitalized COVID-19 patients.¹⁰³ A multidrug therapy of ivermectin, azithromycin, montelukast, and acetylsalicylic acid (TNR4) in 481 patients increased the likelihood of recovery within 14 days, 3.4 times greater than the comparison group;¹⁰⁴ patients treated with TNR4 had 75% and 81% lower risk of being hospitalized or dying, respectively, than the comparison group.¹⁰⁴ A systematic review identified montelukast as a potential adjuvant therapy for COVID-19.¹⁰⁵ In a prospective, randomized controlled study, high doses of montelukast reduced the risk of respiratory failure in COVID-19 patients and shortened hospital stay.¹⁰⁶ Montelukast may block leukotriene receptors in different organs or act indirectly by inhibiting the nuclear factor kappa B signaling pathway.¹⁰⁷ Moreover, it inhibited plasma-induced platelet activation in COVID-19 patients.¹⁰⁸

3.3.2. Zafirlukast

In a pilot randomized clinical trial of 40 moderate COVID-19 patients, the zafirlukast-treated group did not significantly improve symptom resolution compared to the placebo group.⁶⁶

3.4. Aspirin

Aspirin (acetylsalicylic acid) is a type of NSAID. Many clinical studies of aspirin reported conflicting results

regarding its clinical benefits for COVID-19 patients. Patients taking aspirin often have associated COVID-19 risk factors.¹⁰⁹ In contrast, other studies reported that aspirin was associated with a decreased susceptibility to SARS-CoV-2 infection (OR: 0.92; 95% CI: 0.86–0.98).¹¹⁰ Daily low-dose aspirin significantly reduced the risk of type 2 diabetes associated with COVID-19.¹¹¹ Aspirin was found significantly associated with reduced thromboembolism (OR: 0.163; $p=0.020$);¹¹² aspirin and enoxaparin were associated with reduced mechanical ventilation (OR: 0.032; 95% CI: 0.004–0.226; $p=0.001$).¹¹² A retrospective study found decreased risk of mechanical ventilation ($p=0.007$), ICU admission ($p=0.005$), and in-hospital mortality ($p=0.02$) among patients treated with aspirin.¹¹³ A retrospective study found aspirin use associated with decreased mortality ($p=0.046$) in hospitalized COVID-19 patients.¹¹⁴ Two meta-analysis studies found that aspirin reduces all-cause mortality in COVID-19 patients.^{115,116} A systematic review and meta-analysis of 34,415 COVID-19 patients found that aspirin was significantly associated with reduced mortality;¹¹⁷ a systematic review and meta-analysis encompassing 164,539 COVID-19 patients found that low-dose aspirin was associated with reduced in-hospital mortality.¹¹⁸ A retrospective study of 2,070 critically ill COVID-19 patients found that aspirin treatment was associated with lower mortality (hazard ratio: 0.57; 95% CI: 0.41–0.78).¹¹⁹ A retrospective study of 35,370 veterans with COVID-19 found pre-existing aspirin prescription was associated with decreased mortality at 14 (OR: 0.38; 95% CI: 0.32–0.46) and 30 days (OR: 0.38; 95% CI: 0.33–0.45).¹²⁰ Moreover, a study of 21,579 COVID-19 patients found that aspirin treatment was associated with low mortality ($p=0.01$), reduced hazard for progression to severe disease or death ($p=0.02$), and increased hospital-free days ($p=0.01$).¹²¹ A propensity score-matched retrospective study of 2,785 COVID-19 patients found low in-hospital death (hazard ratio: 0.518; 95% CI: 0.308–0.872).¹²² In addition, several meta-analyses found that aspirin was associated with reduced mortality.^{116,123–125} A clinical trial of 14,892 hospitalized COVID-19 patients found a slightly shorter hospitalization duration (8 vs. 9 days) with low-dose aspirin.¹²⁶ Propensity score-matched cohort analyses found that aspirin treatment was associated with a lower risk of in-hospital mortality¹²⁷ (hazard ratio: 0.62; 95% CI: 0.42–0.9; $p=0.018$).¹²⁸ A meta-analysis found a lower likelihood of death in aspirin-treated versus non-aspirin-treated COVID-19 patients.¹²⁹ Other studies found that aspirin use was not associated with SARS-CoV-2 infection.¹³⁰ A retrospective study of 1,190 critically ill COVID-19 patients found that aspirin use was associated with less

frequent deep vein thrombosis ($p<0.001$), pulmonary embolism ($p<0.001$), stroke ($p=0.001$), acute respiratory distress syndrome ($p<0.001$), and mortality ($p<0.001$).¹³¹ In a clinical trial (India: CTRI/2021/06/034254) involving 260 patients with mild-to-moderate COVID-19, APMV2020 (aspirin and promethazine) improved patient symptoms ($p<0.05$).¹³² Aspirin combined with famotidine exhibited a significant synergistic survival benefit (OR: 0.55; 95% CI: 0.39–0.78), with a 32.5% reduction in the RR of death.⁵⁶

Additional clinical studies reported no benefits for COVID-19 patients treated with aspirin. A retrospective study of 262 hospitalized COVID-19 patients found no benefits for aspirin use.¹³³ Aspirin in hospitalized patients with mild-to-moderate COVID-19 did not prevent clinical deterioration.¹³⁴ A retrospective study of 125 COVID-19 patients found no protective effect of daily aspirin on mortality, mechanical ventilation, or progression to ICU-level care.¹³⁵ A retrospective study of 28,856 COVID-19 patients found no significant association between aspirin use and 30-day mortality.¹³⁶ Clinical trial NCT04381936 involving 22,560 COVID-19 hospitalized patients found a slightly shorter duration of hospitalization ($p=0.0062$) and reduction in thrombotic events (4.6% in the aspirin-treated group vs. 5.3% in the SOC group), but with no association to reductions in mortality at 28 days, progression to mechanical ventilation or death, and an increase in major bleeding events (1.6% in the aspirin-treated group vs. 1.0% in the SOC group) among those treated with aspirin.¹³⁷ A retrospective study of 491 hospitalized COVID-19 patients found no impact of aspirin treatment on group outcomes.¹³⁸ For COVID-19 patients with coronary artery disease, low-dose aspirin was not correlated with all-cause mortality.¹³⁹ A propensity-matched analysis found no effect of aspirin on mortality for hospitalized COVID-19 patients.¹⁴⁰ A retrospective study of 31.1 million patients found no association for low-dose aspirin with risk of hospitalization and death/intubation.¹⁴¹

Other clinical studies identified increased risks of adverse events in COVID-19 patients associated with aspirin. A retrospective study of 376 patients, including 128 on aspirin, found a significantly shorter mechanical ventilation duration ($p=0.04$) but a significantly longer hospitalization (5.5 days in the aspirin-treated group vs. 4 days in the non-aspirin group, $p=0.01$).¹⁴² A systematic review and meta-analysis found no association between aspirin use and reduced all-cause mortality, but a higher risk of bleeding (OR: 1.72; 95% CI: 1.32–2.24).¹⁴³ An observational cohort study found that aspirin use was associated with arterial line failure ($p=0.02$) in ICU-

bound COVID-19 patients.¹⁴⁴ A meta-analysis of three studies with 1,054 patients found increased risk for mortality among aspirin users (22.6% among aspirin users vs. 18.3% among non-aspirin users).¹⁰⁹ A retrospective study of 1,357 older COVID-19 patients (age 75 or older) found that aspirin use was associated with increased mortality and a longer hospital stay;¹⁴⁵ a study of geriatric COVID-19 patients found similar results.¹⁴⁶ A retrospective study of 22,660 patients found that aspirin use before COVID-19 was associated with increased mortality, and aspirin use during COVID-19 was associated with a higher risk of conventional oxygen therapy.¹⁴⁷ A retrospective study of 13,585 COVID-19 patients taking aspirin for cardioprotection had a significantly higher risk of hospitalization.¹⁴⁸ A retrospective study of 334,374 veterans with COVID-19 found pre-existing aspirin prescription associated with significant decreased risk of post COVID-19 thromboembolic disorders, including pulmonary embolism (OR: 0.76; 95% CI: 0.69–0.83) but an increased risk of acute arterial diseases, including ischemic stroke (OR: 1.54; 95% CI: 1.46–1.60), and acute ischemic heart disease (OR: 1.33; 95% CI: 1.26–1.39).¹⁴⁹ A study of rivaroxaban and aspirin was discontinued in clinical trial NCT04324463 due to increased risk of bleeding.¹⁵⁰ A retrospective study of 390 COVID-19 patients found that past aspirin use was a major risk factor for COVID-19 mortality ($p=0.0003$).¹⁵¹ A retrospective study found an inverse association between the likelihood of COVID-19 infection, disease duration, and mortality with aspirin use.¹⁵² In a retrospective case–control study of 3,712 COVID-19 patients, aspirin was associated with an increased risk of mortality.⁶⁵ A *post hoc* analysis found that aspirin use was associated with persistent (adjusted OR: 1.38; 95% CI: 1.06–1.81) and new lymphopenia (adjusted OR: 2.57; 95% CI: 1.26–5.26) in severe COVID-19 patients.¹⁵³

4. Discussion

Consistent with the mast cell-targeting hypothesis, clinical benefits in COVID-19 patients have been reported with adjunctive treatments, including fluvoxamine and cyproheptadine,⁵⁹ hydroxyzine,⁶¹ one of (dexchlorpheniramine, cetirizine, loratadine, or ebastine) combined with azithromycin,²³ loratadine,⁶⁵ azelastine,^{19,20} high-dose famotidine,^{1,43,44} high-dose famotidine and celecoxib,^{49,50} and famotidine combined with aspirin.⁵⁶ It is unknown if normal-dose famotidine contributed to the observed clinical benefits when combined with cetirizine²² over possible benefits from cetirizine alone. Based on the clinical benefits associated with high-dose famotidine,^{1,43–45}

it is strongly recommended that future clinical studies evaluate cetirizine coadministered with high-dose famotidine for treating COVID-19 patients as adjunctive treatments. Positive clinical results have been reported for 28 patients for the high-dose famotidine and celecoxib;^{49,50} the rationale for selecting celecoxib was based on SARS-CoV-1 articles that have since been retracted.^{154,155} The mast cell stabilizer quercetin treatment of COVID-19 patients is associated with clinical benefits in multiple studies.^{88–92,94} The mast cell stabilizer luteolin is associated with clinical benefits for treating persistent COVID-19 olfactory dysfunction.^{80–82} Mixed results were reported for the normal (heartburn) dose of famotidine and aspirin. Effective dose levels vary by treatment, with the threshold dose level for some treatments, such as cimetidine, being too high for targeting histamine receptors on mast cells, other immune cells, and platelets.¹ Candidate adjunctive treatments targeting mast cells with associated clinical benefits are summarized in [Tables 1 and 2](#).

Clinical trials evaluating candidate adjunctive treatments were conducted alongside current standard-of-care therapies to ensure that patients continue to receive established COVID-19 treatments and are not disadvantaged. During the COVID-19 pandemic, shifting current standards-of-care levels negatively impacted clinical trials for high-dose famotidine combined with hydroxychloroquine (public perceptions negatively affecting enrollment) or remdesivir in clinical trial NCT04370262¹ and high-dose famotidine and celecoxib with dexamethasone in clinical trial NCT04488081,⁵⁵ even with known drug–drug interactions between celecoxib and dexamethasone.^{52,54} Concomitant treatment of COVID-19 patients with both celecoxib (NSAID) and dexamethasone (potent steroidal anti-inflammatory drug) was considered contraindicated because the combination may cause excessive immunosuppression during active SARS-CoV-2 infection.

The main focus of this study was the modulation of mast cells by antihistamines, mast cell stabilizers, and leukotriene receptor antagonists; many of these drugs, with reports of beneficial clinical effects in COVID-19 patients, have alternative mechanisms of action that could account for these benefits. Aspirin inhibits cyclooxygenase-1 and -2 enzymes, reducing the production of prostaglandins (inflammatory mediators that reduce pain and fever and promote platelet aggregation), thereby reducing the risk of blood clots. Astemizole can bind to the ACE2 receptor and block SARS-CoV-2 Spike pseudoviruses *in vitro*.¹⁵⁶ Azelastine has anti-inflammatory and *in vitro* antiviral activity against respiratory viruses, including SARS-CoV-2.^{157–159} *In vitro*, chlorpheniramine maleate

Table 1. Promising adjunctive COVID-19 treatments targeting mast cell activation

Treatments	References	N	Findings	Benefits
Azelastine	19	90	Not available	Faster negative COVID-19 test results
	20	251	$p=0.0041$	Reduced viral load in outpatients
	21	450	OR: 0.31	Reduced SARS-CoV-2 infections
Cetirizine, dexchlorpheniramine, ebastine, or loratadine	23	84 elderly	Not available	No deaths in 2020
	62	468	Hospitalization ($p=0.001$)	Reduced hospitalization and deaths
Cetirizine and famotidine	22	110	Not available	Reduced pulmonary symptoms
Chlorpheniramine maleate nasal spray	58	101	$p<0.05$	Improved rate of clinical recovery
Cyproheptadine and fluvoxamine	59	147	$p<0.001$	The treated patients did not clinically deteriorate
High-dose famotidine	45	20	LDH: $p=0.01$, WBC: $p=0.04$, length of stay: $p=0.04$, oxygen saturation: $p=0.01$, cough: $p=0.02$	Improved clinical results
High-dose famotidine and celecoxib	49,50	28	Not available	Improved clinical results
Famotidine and aspirin	56	832	OR: 0.55; 95% CI: 0.39–0.78	Significant synergistic survival benefit
Hydroxyzine	61	164	AOR: 0.51; 95% CI: 0.29–0.88; $p=0.016$	Reduced mortality
Loratadine	65		OR: 0.20; 95% CI: 0.02–0.93	Reduced mortality
Luteolin	84	42	Reduced symptom severity $p=0.0118$ & shortened time to testing negative $p=0.0002$	Reduced symptom severity and shortened time to testing negative
Quercetin	88	100	Recovery: $p=0.0004$, acute symptoms resolution: $p=0.0051$	Speedy recovery and improved resolution of acute symptoms
	94	544	Hospitalization (RR: 0.30; 95% CI: 0.14–0.62), ICU admission (RR: 0.27; 95% CI: 0.09–0.78), mortality (RR: 0.18; 95% CI: 0.03–0.98)	Decreased the risk of hospital admission by 70%, ICU admission by 73%, and mortality by 82% versus control
	95	60	Partial earlier discharge $p=0.039$, reduced ALP $p=0.002$, q-CRP $p=0.004$, & LDH $p=0.032$	Partial earlier discharge, reduced ALP, q-CRP, and LDH
Quercetin, curcumin, and vitamin D3	91	50	Negative testing: $p=0.009$	Expedited negative testing for SARS-CoV-2 and rapid resolution of acute symptoms

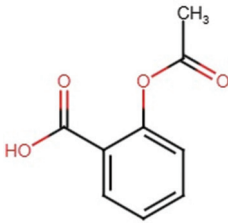
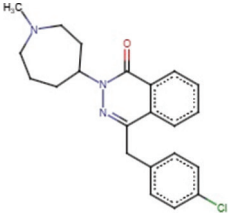
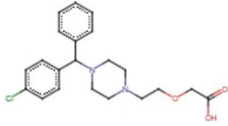
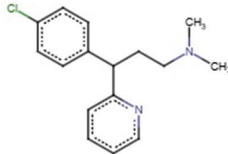
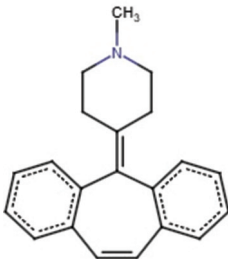
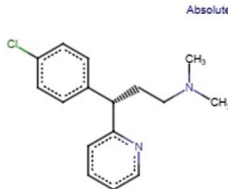
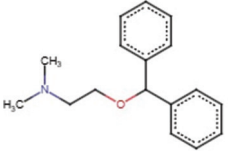
Abbreviations: ALP: Alkaline phosphatase; AOR: Adjusted odds ratio; CI: Confidence interval; CRP: C-reactive protein; ICU: Intensive care unit; LDH: Lactate dehydrogenase; OR: Odds ratio; RR: Relative risk; WBC: Whole blood count.

reduced the viral load in SARS-CoV-2-infected Vero 76 (human kidney) cells.¹⁶⁰ Ebastine also possesses anti-inflammatory effects. In a mouse model, intraperitoneal famotidine exhibited anti-inflammatory effects (vagus nerve inflammatory reflex) that were not mast cell-dependent.¹⁶¹ *In vitro*, hydroxyzine inhibited ACE2 receptor binding by SARS-CoV-2 Spike protein.¹⁶² *In vitro*, ketotifen, in combination with indomethacin or naproxen, reduced viral yield with an additive or synergistic effect.¹⁶³ *In vitro*, the treatments loratadine and desloratadine blocked SARS-CoV-2 binding to ACE2;¹⁶⁴ desloratadine blocked viral entry into human nasal epithelial cells.¹⁶⁵ Luteolin, an antiviral, antioxidant, anti-inflammatory, and anti-cancer agent, acts by scavenging reactive oxygen

species, inhibiting cyclooxygenases (inflammatory enzymes), and modulating multiple signaling pathways. Quercetin is an antioxidant that inhibits inflammatory pathways, modulates multiple signaling pathways, and has potential antiviral activity.¹⁶⁶ *In vitro*, nilotinib inhibited SARS-CoV-2 in green monkey kidney Vero-E6 and Calcu-3 (human lung adenocarcinoma epithelial) cells.¹⁶⁷

This study possesses several limitations. Clinical results across studies may vary by COVID-19 disease severity, patient demographics, differences in comorbidities, concomitant medications, and the standard-of-care treatments included in the studies. Moreover, literature not indexed in PubMed, DOAJ, or Europe PMC was excluded from this review.

Table 2. Candidate mast cell targeting compounds with beneficial clinical results

Drug	Structure	Pros/Cons	Preventative	Mild-to-moderate	Severe	Mortality
Aspirin		Pro Con	110 152	112,113,131 143,148,152	126 142,144-147,149,150,153	56,113-122,127-129,131 65,109,145,146,151,152
Azelastine		Pro	20,21,67	19	-	-
Cetirizine		Pro	67	22	-	23
Chlorpheniramine		Pro	-	57,58	-	-
Cyproheptadine		Pro	-	59	-	-
Dexchlorpheniramine		Pro	-	-	-	23
Diphenhydramine		Pro	67	-	-	-

(Cont'd...)

Table 2. (Continued)

Drug	Structure	Pros/Cons	Preventative	Mild-to-moderate	Severe	Mortality
Ebastine		Pro	-	-	-	23
Famotidine high-dose (HD)		Pro	-	1,43-45	HD famotidine and celecoxib ^{49,50}	Famotidine and aspirin ⁵⁶
Hydroxyzine		Pro	67	-	-	61
Loratadine		Pro	67	-	-	23,65
Luteolin		Pro	-	84	-	-
Montelukast		Pro Con	- -	99-104,106 98	- -	104 -
Quercetin		Pro	85	88-92,94,97	-	94

Notes: Compound structures were generated using the Chemical Sketch Tool; “-” indicates data not available. “Pro” indicates reported clinical benefit; “Con” indicates adverse outcomes. “Preventative” refers to treatment administered before infection. “Mild-to-moderate” refers to mild-to-moderate COVID-19. “Severe” refers to severe COVID-19. “Mortality” refers to treatment effects on patient mortality.

5. Conclusion

Clinical benefits in COVID-19 patients have been reported for the flavonoid mast cell stabilizer quercetin; for several antihistamines (azelastine, cetirizine, chlorpheniramine,

diphenhydramine, hydroxyzine, and loratadine); for ciproheptadine plus fluvoxamine; for azithromycin combined with an antihistamine (dexchlorpheniramine, cetirizine, loratadine, or ebastine); and for famotidine-based regimens (cetirizine plus famotidine and high-

dose famotidine). Positive results have been reported for combination adjunctive treatments, such as high-dose famotidine with celecoxib, and mortality benefits with famotidine and aspirin. However, mixed and conflicting results have been reported for aspirin in multiple COVID-19 clinical studies, with likely increased risks for geriatric patients. Treatments with observed clinical benefits in COVID-19 patients targeting mast cells and histamine receptors warrant follow-up clinical studies as adjunctive treatments. Clinical studies evaluating combinations of these adjunctive treatments in COVID-19 patients are strongly encouraged.

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Conflict of interest

The author declares no conflict of interest.

Author contributions

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References

- Malone RW, Tisdall P, Fremont-Smith P, *et al.* COVID-19: Famotidine, histamine, mast cells, and mechanisms. *Front Pharmacol.* 2021;12:633680.
doi: 10.3389/fphar.2021.633680
- Fremont-Smith M, Gherlone N, Smith N, Tisdall P, Ricke DO. Models for COVID-19 early cardiac pathology following SARS-CoV-2 infection. *Int J Infect Dis.* 2021;113:331-335.
doi: 10.1016/j.ijid.2021.09.052
- Ricke DO, Gherlone N, Fremont-Smith P, Tisdall P, Fremont-Smith M. Kawasaki disease, multisystem inflammatory syndrome in children: Antibody-induced mast cell activation hypothesis. *J Pediatr Pediatr Med.* 2020;4(2):1-7.
doi: 10.29245/2578-2940/2020/2.1157
- Ricke DO, Smith N. VAERS vasculitis adverse events retrospective study: Etiology model of immune complexes activating Fc receptors in Kawasaki disease and multisystem inflammatory syndromes. *Life (Basel).* 2024;14(3):353.
doi: 10.3390/life14030353
- Yu F, Liu X, Ou H, *et al.* The histamine receptor H1 acts as an alternative receptor for SARS-CoV-2. *mBio.* 2024;15(8):e0108824.
doi: 10.1128/mbio.01088-24
- Wu ML, Liu FL, Sun J, *et al.* SARS-CoV-2-triggered mast cell rapid degranulation induces alveolar epithelial inflammation and lung injury. *Signal Transduct Target Ther.* 2021;6(1):428.
doi: 10.1038/s41392-021-00849-0
- Hafezi B, Chan L, Knapp JP, *et al.* Cytokine storm syndrome in SARS-CoV-2 infections: A functional role of mast cells. *Cells.* 2021;10(7):1761.
doi: 10.3390/cells10071761
- Cao JB, Zhu ST, Huang XS, *et al.* Mast cell degranulation-triggered by SARS-CoV-2 induces tracheal-bronchial epithelial inflammation and injury. *Virol Sin.* 2024;39(2):309-318.
doi: 10.1016/j.virs.2024.03.001
- Hu Z, Song C, Xu C, *et al.* Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci.* 2020;63(5):706-711.
doi: 10.1007/s11427-020-1661-4
- Tian S, Hu N, Lou J, *et al.* Characteristics of COVID-19 infection in Beijing. *J Infect.* 2020;80(4):401-406.
doi: 10.1016/j.jinf.2020.02.018
- Basso C, Leone O, Rizzo S, *et al.* Pathological features of COVID-19-associated myocardial injury: A multicentre cardiovascular pathology study. *Eur Heart J.* 2020;41(39):3827-3835.
doi: 10.1093/eurheartj/ehaa664
- Bearse M, Hung YP, Krauson AJ, *et al.* Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19. *Mod Pathol.* 2021;34(7):1345-1357.
doi: 10.1038/s41379-021-00790-1
- Darby JB, Jackson JM. Kawasaki disease and multisystem inflammatory syndrome in children: An overview and comparison. *Am Fam Physician.* 2021;104(3):244-252.
- Patel P, DeCuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED. Clinical characteristics of multisystem inflammatory syndrome in adults: A systematic review. *JAMA Netw Open.* 2021;4(9):e2126456.
doi: 10.1001/jamanetworkopen.2021.26456

15. Dufort Elizabeth M, Koumans Emilia H, Chow Eric J, *et al.* Multisystem inflammatory syndrome in children in New York State. *N Engl J Med.* 2020;383(4):347-358.
doi: 10.1056/NEJMoa2021756
16. Feldstein Leora R, Rose Erica B, Horwitz Steven M, *et al.* Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med.* 2020;383(4):334-346.
doi: 10.1056/NEJMoa2021680
17. Ricke DO. Cardiac adverse events post-vaccination. *Brain Heart.* 2025;3(2):1-15.
doi: 10.36922/bh.5747
18. Ricke DO. Vaccine-associated Kawasaki disease in children. *Microbes Immun.* 2025.
doi: 10.36922/MI025200044
19. Klusmann JP, Grosheva M, Meiser P, *et al.* Early intervention with azelastine nasal spray may reduce viral load in SARS-CoV-2 infected patients. *Sci Rep.* 2023;13(1):6839.
doi: 10.1038/s41598-023-32546-z
20. Meiser P, Flegel M, Holzer F, *et al.* Azelastine nasal spray in non-hospitalized subjects with mild COVID-19 infection: A randomized placebo-controlled, parallel-group, multicentric, phase II clinical trial. *Viruses.* 2024;16(12):1914.
doi: 10.3390/v16121914
21. Lehr T, Meiser P, Selzer D, *et al.* Azelastine nasal spray for prevention of SARS-CoV-2 infections: A phase 2 randomized clinical trial. *JAMA Intern Med.* 2025;185(11):1309-1317.
doi: 10.1001/jamainternmed.2025.4283
22. Hogan RB 2nd, Hogan RB 3rd, Cannon T, *et al.* Dual-histamine receptor blockade with cetirizine - famotidine reduces pulmonary symptoms in COVID-19 patients. *Pulm Pharmacol Ther.* 2020;63:101942.
doi: 10.1016/j.pupt.2020.101942
23. Morán Blanco JI, Alvarenga Bonilla JA, Homma S, Suzuki K, Fremont-Smith P, Villar Gómez de Las Heras K. Antihistamines and azithromycin as a treatment for COVID-19 on primary health care - A retrospective observational study in elderly patients. *Pulm Pharmacol Ther.* 2021;67:101989-101989.
doi: 10.1016/j.pupt.2021.101989
24. Matsumori A, Yamamoto K, Shimada M. Cetirizine a histamine H1 receptor antagonist improves viral myocarditis. *J Inflamm Lond Engl.* 2010;7:39-39.
doi: 10.1186/1476-9255-7-39
25. Freedberg DE, Conigliaro J, Wang TC, *et al.* Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. *Gastroenterology.* 2020;159(3):1129-1131.e3.
doi: 10.1053/j.gastro.2020.05.053
26. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. *Am J Gastroenterol.* 2020;115(10):1617-1623.
doi: 10.14309/ajg.0000000000000832
27. Pahwani S, Kumar M, Aperia F, *et al.* Efficacy of oral famotidine in patients hospitalized with severe acute respiratory syndrome coronavirus 2. *Cureus.* 2022;14(2):e22404.
doi: 10.7759/cureus.22404
28. Chowdhury ATMM, Kamal A, Abbas MKU, *et al.* Role of H2 receptor blocker famotidine over the clinical recovery of COVID-19 patients: A randomized controlled trial. *World J Clin Cases.* 2022;10(23):8170.
doi: 10.12998/wjcc.v10.i23.8170
29. Wagner JJ, St. Cyr N, Douen A, Fogel J, Trillo J. A retrospective analysis of clinical outcomes between hospitalized patients with COVID-19 who received famotidine or pantoprazole. *JGH Open.* 2023;7(7):464-469.
doi: 10.1002/jgh3.12905
30. Kwon R, Kim HJ, Lee SW, *et al.* Effectiveness of famotidine on the risk of poor prognosis in patients with COVID-19: A nationwide cohort study in Korea. *Heliyon.* 2023;9(6):e16171.
doi: 10.1016/j.heliyon.2023.e16171
31. Razjouyan J, Helmer DA, Lynch KE, *et al.* Smoking status and factors associated with COVID-19 in-hospital mortality among US veterans. *Nicotine Tob Res.* 2022;24(5):785-793.
doi: 10.1093/ntr/ntab223
32. Chiu L, Shen M, Lo CH, *et al.* Effect of famotidine on hospitalized patients with COVID-19: A systematic review and meta-analysis. *PLoS One.* 2021;16(11):e0259514.
doi: 10.1371/journal.pone.0259514
33. Cheung KS, Hung IFN, Leung WK. Association between famotidine use and COVID-19 severity in Hong Kong: A territory-wide study. *Gastroenterology.* 2021;160(5):1898-1899.
doi: 10.1053/j.gastro.2020.05.098
34. Sun C, Chen Y, Hu L, *et al.* Does famotidine reduce the risk of progression to severe disease, death, and intubation for COVID-19 patients? A systemic review and meta-analysis. *Dig Dis Sci.* 2021;66(11):3929-3937.
doi: 10.1007/s10620-021-06872-z
35. Kuno T, So M, Takahashi M, Egorova NN. The association between famotidine and in-hospital mortality of patients with COVID-19. *J Med Virol.* 2022;94(3):1186-1189.
doi: 10.1002/jmv.27375
36. Fung KW, Baik SH, Baye F, Zheng Z, Huser V,

- McDonald CJ. Effect of common maintenance drugs on the risk and severity of COVID-19 in elderly patients. *PLoS One*. 2022;17(4):e0266922.
doi: 10.1371/journal.pone.0266922
37. Balouch B, Vontela S, Yeakel H, Alnouri G, Sataloff RT. Role of famotidine and other acid reflux medications for SARS-CoV-2: A pilot study. *J Voice*. 2023;37(3):419-425.
doi: 10.1016/j.jvoice.2021.01.007
 38. Cheema HA, Shafiee A, Athar MMT, et al. No evidence of clinical efficacy of famotidine for the treatment of COVID-19: A systematic review and meta-analysis. *J Infect*. 2023;86(2):154-225.
doi: 10.1016/j.jinf.2022.11.022
 39. Amjad W, Kamal F, Malik A, Singh R, Mahmood S. Histamine 2 receptor antagonists do not improve the outcomes of hospitalized COVID-19 patients. *Prz Gastroenterol*. 2022;17(2):146-151.
doi: 10.5114/pg.2021.107799
 40. Li W, Dong Y, Lei X. No evidence indicates famotidine reduces the risk of serious disease in COVID-19 patients after propensity score matching: Meta-analysis and systematic reviews. *Dig Dis Sci*. 2022;67(1):351-353.
doi: 10.1007/s10620-021-07214-9
 41. Yeramaneni S, Doshi P, Sands K, Cooper M, Kurbegov D, Fromell G. Famotidine use is not associated with 30-day mortality: A coarsened exact match study in 7158 hospitalized patients with coronavirus disease 2019 from a large healthcare system. *Gastroenterology*. 2021;160(3):919-921.e3.
doi: 10.1053/j.gastro.2020.10.011
 42. Kow CS, Abdul Sattar Burud I, Hasan SS. Use of famotidine and risk of severe course of illness in patients with COVID-19: A meta-analysis. *Mayo Clin Proc*. 2021;96(5):1365-1367.
doi: 10.1016/j.mayocp.2021.03.001
 43. Brennan CM, Nadella S, Zhao X, et al. Oral famotidine versus placebo in non-hospitalised patients with COVID-19: A randomised, double-blind, data-intensive, phase 2 clinical trial. *Gut*. 2022;71:879-888.
doi: 10.1136/gutjnl-2022-326952
 44. Janowitz T, Gablenz E, Pattinson D, et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: A case series. *Gut*. 2020;69(9):1592.
doi: 10.1136/gutjnl-2020-321852
 45. Samimagham HR, Hassani Azad M, Haddad M, Arabi M, Hooshyar D, Kazemijahromi M. The efficacy of famotidine in improvement of outcomes in hospitalized COVID-19 patients: A structured summary of a study protocol for a randomised controlled trial. *Trials*. 2020;21(1):848.
doi: 10.1186/s13063-020-04773-6
 46. Sethia R, Prasad M, Mahapatra SJ, et al. Efficacy of Famotidine for COVID-19: A Systematic Review and Meta-Analysis. medRxiv; 2020.
doi: 10.1101/2020.09.28.20203463
 47. Raghavan S, Leo MD. Histamine potentiates SARS-CoV-2 spike protein entry into endothelial cells. *Front Pharmacol*. 2022;13:872736.
doi: 10.3389/fphar.2022.872736
 48. Mukherjee R, Bhattacharya A, Bojkova D, et al. Famotidine inhibits toll-like receptor 3-mediated inflammatory signaling in SARS-CoV-2 infection. *J Biol Chem*. 2021;297(2):100925.
doi: 10.1016/j.jbc.2021.100925
 49. Tomera K, Kittah J. Brief Report: Rapid Clinical Recovery from Severe COVID-19 with High Dose Famotidine and High Dose Celecoxib Adjuvant Therapy. Preprintsorg; 2020.
doi: 10.20944/preprints202008.0519.v1
 50. Tomera KM, Malone RW, Kittah JK. Hospitalized COVID-19 Patients Treated with Celecoxib and High Dose Famotidine Adjuvant Therapy show Significant Clinical Responses. SSRN Prepr; 2020. p. 42.
doi: 10.2139/ssrn.3646583
 51. Theoharides TC, Conti P. Dexamethasone for COVID-19? Not so fast. *J Biol Regul Homeost Agents*. 2020;34(4):1241-1243.
doi: 10.23812/20-EDITORIAL_1-5
 52. Malone R, Tomera K, Egbujiobi L, Kittah J. Famotidine and Celecoxib COVID-19 Treatment Without and With Dexamethasone; Retrospective Comparison of Sequential Continuous Cohorts. United States: Research Square; 2021.
doi: 10.21203/rs.3.rs-526394/v1
 53. Drug Interactions between Celecoxib and Dexamethasone; 2025. Available from: <https://www.drugs.com/drug-interactions/celecoxib-with-dexamethasone-560-0-810-0.html> [Last accessed on 2025 Nov 15].
 54. DrugBank. Celecoxib; 2025. Available from: <https://go.drugbank.com/drugs/DB00482> [Last accessed on 2025 Oct 01].
 55. Files DC, Aggarwal N, Albertson T, et al. Report of the first seven agents in the I-SPY COVID trial: A phase 2, open label, adaptive platform randomised controlled trial. *eClinicalMedicine*. 2023;58:101889.
doi: 10.1016/j.eclinm.2023.101889
 56. Mura C, Preissner S, Nahles S, Heiland M, Bourne PE, Preissner R. Real-world evidence for improved outcomes with histamine antagonists and aspirin in 22,560 COVID-19 patients. *Signal Transduct Target Ther*. 2021;6(1):267.
doi: 10.1038/s41392-021-00689-y

57. Torres J, Go CC, Chohan FA, *et al.* *Chlorpheniramine Maleate Nasal Spray in COVID-19 Patients: Case Series.* United States: Research Square; 2021.
doi: 10.21203/rs.3.rs-138252/v1
58. Valerio-Pascua F, Jackeline E, Tesch ML, *et al.* *Chlorpheniramine Intranasal Spray to Accelerate COVID-19 Clinical Recovery in an Outpatient Setting: The ACCROS Trials.* United States: Research Square; 2022.
doi: 10.21203/rs.3.rs-2167465/v1
59. Wannigama DL, Hurst C, Phattharapornjaroen P, *et al.* Early treatment with fluvoxamine, bromhexine, cyproheptadine, and niclosamide to prevent clinical deterioration in patients with symptomatic COVID-19: A randomized clinical trial. *eClinicalMedicine.* 2024;70:102517.
doi: 10.1016/j.eclinm.2024.102517
60. Boniatti MM, Nedel WL, Rihl MF, *et al.* Effect of cyproheptadine on ventilatory support-free days in critically ill patients with COVID-19: An open-label, randomized clinical trial. *Indian J Crit Care Med.* 2023;27(7):517-521.
doi: 10.5005/jp-journals-10071-24482
61. Sánchez-Rico M, Limosin F, Vernet R, *et al.* Hydroxyzine use and mortality in patients hospitalized for COVID-19: A multicenter observational study. *J Clin Med.* 2021; 10(24):5891.
doi: 10.3390/jcm10245891
62. Morán Blanco JJ, Alvarenga Bonilla JA, Fremont-Smith P, Villar Gómez de las Heras K. Antihistamines as an early treatment for Covid-19. *Heliyon.* 2023;9(5):e15772.
doi: 10.1016/j.heliyon.2023.e15772
63. Pastor-Fernández A, Bertos AR, Sierra-Ramírez A, *et al.* Treatment with the senolytics dasatinib/quercetin reduces SARS-CoV-2-related mortality in mice. *Aging Cell.* 2023;22(3):e13771.
doi: 10.1111/accel.13771
64. Wu ML, Liu FL, Sun J, *et al.* Combinational benefit of antihistamines and remdesivir for reducing SARS-CoV-2 replication and alleviating inflammation-induced lung injury in mice. *Zool Res.* 2022;43(3):457-468.
doi: 10.24272/j.issn.2095-8137.2021.469
65. Villatoro JM, Mejía-Abril G, García LD, *et al.* A case-control of patients with COVID-19 to explore the association of previous hospitalisation use of medication on the mortality of COVID-19 disease: A propensity score matching analysis. *Pharmaceuticals (Basel).* 2022;15(1):78.
doi: 10.3390/ph15010078
66. Ghobain MA, Rebh F, Saad A, *et al.* The efficacy of Zafirlukast as a SARS-CoV-2 helicase inhibitor in adult patients with moderate COVID-19 Pneumonia (pilot randomized clinical trial). *J Infect Public Health.* 2022;15(12):1546-1550.
doi: 10.1016/j.jiph.2022.11.016
67. Reznikov LR, Norris MH, Vashisht R, *et al.* Identification of antiviral antihistamines for COVID-19 repurposing. *Biochem Biophys Res Commun.* 2021;538:173-179.
doi: 10.1016/j.bbrc.2020.11.095
68. Black SD. Molecular modeling and preliminary clinical data suggesting antiviral activity for chlorpheniramine (chlorphenamine) against COVID-19. *Cureus.* 2022;14(1):e20980.
doi: 10.7759/cureus.20980
69. Berkowitz RL, Bluhm AP, Knox GW, McCurdy CR, Ostrov DA, Norris MH. Sigma receptor ligands prevent COVID mortality *in vivo*: Implications for future therapeutics. *Int J Mol Sci.* 2023;24(21):15718.
doi: 10.3390/ijms242115718
70. Panse S, Kanchi M, Chacko J, *et al.* Intensive care unit setup for COVID-19. *J Cardiac Critical Care TSS.* 2020;4(1):5-11.
doi: 10.1055/s-0040-1713548
71. May BC, Gallivan KH. Levocetirizine and montelukast in the COVID-19 treatment paradigm. *Int Immunopharmacol.* 2022;103:108412.
doi: 10.1016/j.intimp.2021.108412
72. Kim B, Jung JH, Han K, *et al.* Histamine-2 receptor antagonists and proton pump inhibitors are associated with reduced risk of SARS-CoV-2 infection without comorbidities including diabetes, hypertension, and dyslipidemia: A propensity score-matched nationwide cohort study. *J Korean Med Sci.* 2023;38(13):e99.
doi: 10.3346/jkms.2023.38.e99
73. Fan X, Liu Z, Miyata T, *et al.* Effect of acid suppressants on the risk of COVID-19: A propensity score-matched study using UK biobank. *Gastroenterology.* 2021;160(1): 455-458.e5.
doi: 10.1053/j.gastro.2020.09.028
74. Puigdemívol-Sánchez A, Juanes-González M, Calderón-Valdiviezo A, *et al.* COVID-19 in relation to chronic antihistamine prescription. *Microorganisms.* 2024;12(12):2589.
doi: 10.3390/microorganisms12122589
75. Redondo-Sendino Á, González Sánchez IC, de Victoria Fernández B. Skin manifestations associated with the new coronavirus SARS-CoV-2 disease. *Med Clin Engl Ed.* 2020;155(9):414-415.
doi: 10.1016/j.medcle.2020.04.026
76. Criado PR, Criado RFJ, Pincelli TP, Yoshimoto TA, Naufal GGA, Abdalla BMZ. Chronic spontaneous urticaria exacerbation in a patient with COVID-19: Rapid and excellent response to omalizumab. *Int J Dermatol.*

- 2020;59(10):1294-1295.
doi: 10.1111/ijid.15134
77. Tesch ML, Dasgupta R, Khawaja UA, Sanchez-Gonzalez M, Franck R. Chlorpheniramine maleate throat spray for the treatment of COVID-19-induced acute viral pharyngitis: Case series. *Cureus*. 2023;15(1):e34310.
doi: 10.7759/cureus.34310
78. Yi L, Li Z, Yuan K, *et al*. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. *J Virol*. 2004;78(20):11334-11339.
doi: 10.1128/jvi.78.20.11334-11339.2004
79. Umsumarng S, Dissook S, Arjsri P, *et al*. Inhibitory effect of luteolin on spike S1 glycoprotein-induced inflammation in THP-1 cells via the ER stress-inducing calcium/CHOP/MAPK pathway. *Pharmaceuticals (Basel)*. 2024;17(10):402.
doi: 10.3390/ph17101402
80. Di Stadio A, Gallina S, Cocuzza S, *et al*. Treatment of COVID-19 olfactory dysfunction with olfactory training, palmitoylethanolamide with luteolin, or combined therapy: A blinded controlled multicenter randomized trial. *Eur Arch Otorhinolaryngol*. 2023;280(11):4949-4961.
doi: 10.1007/s00405-023-08085-8
81. Di Stadio A, Cantone E, De Luca P, *et al*. Parosmia COVID-19 related treated by a combination of olfactory training and ultramicrosized PEA-LUT: A prospective randomized controlled trial. *Biomedicines*. 2023;11(4):1109.
doi: 10.3390/biomedicines11041109
82. Cantone E, D'Ascanio L, De Luca P, *et al*. Persistent COVID-19 parosmia and olfactory loss post olfactory training: Randomized clinical trial comparing central and peripheral-acting therapeutics. *Eur Arch Otorhinolaryngol*. 2024;281(7):3671-3678.
doi: 10.1007/s00405-024-08548-6
83. Lee S, Kim JH, Kim C, Jung W, Park J, Park J. Luteolin-7-O-glucoside from *Elsholtzia ciliata* extract inhibits the replication of coronavirus. *PLoS One*. 2025;20(6):e0325371.
doi: 10.1371/journal.pone.0325371
84. Di Pierro F, Iqtadar S, Khan A, *et al*. Potential clinical benefits of quercetin in the early stage of COVID-19: Results of a second, pilot, randomized, controlled and open-label clinical trial. *Int J Gen Med*. 2021;14:2807-2816.
doi: 10.2147/ijgm.s318949
85. Rondanelli M, Perna S, Gasparri C, *et al*. Promising effects of 3-month period of quercetin phytosome® supplementation in the prevention of symptomatic COVID-19 disease in healthcare workers: A pilot study. *Life (Basel)*. 2022;12(1):66.
doi: 10.3390/life12010066
86. Arslan B, Ergun NU, Topuz S, *et al*. Synergistic effect of quercetin and vitamin C against COVID-19: Is a possible guard for front liners. *SSRN*. Published online 2020. Available from: <https://europepmc.org/article/ppr/ppr239932>
87. Tylishchak Z, Pryshliak O, Boichuk O, *et al*. Effectiveness of the quercetin use in patients with COVID-19 with concomitant type 2 diabetes mellitus. *Wiad Lek*. 2024;77(10):1962-1968.
doi: 10.36740/wlek/191875
88. Di Pierro F, Khan A, Iqtadar S, *et al*. Quercetin as a possible complementary agent for early-stage COVID-19: Concluding results of a randomized clinical trial. *Front Pharmacol*. 2023;13:1096853.
doi: 10.3389/fphar.2022.1096853
89. Di Pierro F, Derosa G, Maffioli P, *et al*. Possible therapeutic effects of adjuvant quercetin supplementation against early-stage COVID-19 infection: A prospective, randomized, controlled, and open-label study. *Int J Gen Med*. 2021;8(14):2359-2366.
doi: 10.2147/ijgm.s318720
90. Ujjan ID, Khan S, Nigar R, Ahmed H, Ahmad S, Khan A. The possible therapeutic role of curcumin and quercetin in the early-stage of COVID-19-Results from a pragmatic randomized clinical trial. *Front Nutr*. 2023;9:1023997.
doi: 10.3389/fnut.2022.1023997
91. Khan A, Iqtadar S, Mumtaz SU, *et al*. Oral co-supplementation of curcumin, quercetin, and vitamin D3 as an adjuvant therapy for mild to moderate symptoms of COVID-19-results from a pilot open-label, randomized controlled trial. *Front Pharmacol*. 2022;13:898062.
doi: 10.3389/fphar.2022.898062
92. Önal H, Arslan B, Ergun NÜ, *et al*. Treatment of COVID-19 patients with quercetin: A prospective, single center, randomized, controlled trial. *Turk J Biol*. 2021;45(4):518-529.
doi: 10.3906/biy-2104-16
93. Wu W, Wang W, Liang L, *et al*. Treatment with quercetin inhibits SARS-CoV-2 N protein-induced acute kidney injury by blocking Smad3-dependent G1 cell-cycle arrest. *Mol Ther*. 2023;31(2):344-361.
doi: 10.1016/j.ymthe.2022.12.002
94. Ziaei S, Alimohammadi-Kamalabadi M, Hasani M, Malekahmadi M, Persad E, Heshmati J. The effect of quercetin supplementation on clinical outcomes in COVID-19 patients: A systematic review and meta-analysis. *Food Sci Nutr*. 2023;11(12):7504-7514.
doi: 10.1002/fsn3.3715
95. Shohan M, Nashibi R, Mahmoudian-Sani MR, *et al*. The therapeutic efficacy of quercetin in combination with antiviral drugs in hospitalized COVID-19 patients: A randomized

- controlled trial. *Eur J Pharmacol.* 2022;914:174615.
doi: 10.1016/j.ejphar.2021.174615
96. Roy AV, Chan M, Banadyga L, *et al.* Quercetin inhibits SARS-CoV-2 infection and prevents syncytium formation by cells co-expressing the viral spike protein and human ACE2. *Virol J.* 2024;21(1):29.
doi: 10.1186/s12985-024-02299-w
97. Al-Juhaishi AMR, Aal-Aaboda M, Mosa AU. Effects of cranberry on outpatients with mild to moderate COVID-19 infection. *Iraqi J Pharm Sci.* 2024;32(3):165-171.
doi: 10.31351/vol32iss3pp165-171
98. Rothman RL, Stewart TG, Mourad A, *et al.* Time to sustained recovery among outpatients with COVID-19 receiving montelukast vs placebo: The ACTIV-6 randomized clinical trial. *JAMA Netw Open.* 2024;7(10):e2439332.
doi: 10.1001/jamanetworkopen.2024.39332
99. Khan AR, Misdary C, Yegya-Raman N, *et al.* Montelukast in hospitalized patients diagnosed with COVID-19. *J Asthma.* 2021;59(4):780-786.
doi: 10.1080/02770903.2021.1881967
100. Pourahmad M, Aria A, Momenzadeh M, *et al.* Evaluation of the effect of montelukast drug in improving the clinical condition of patients with COVID-19 in referral hospitals in Isfahan; a randomized clinical trial. *J Nephropharmacol.* 2024;13(2):e11650.
doi: 10.34172/npj.2023.11650
101. Jahangirifard A, Fani K, Mirtajani SB. The effect of bromelain combined with montelukast in hospitalized COVID-19 patients. *Int J Basic Sci Med.* 2023;8(1):36-41.
doi: 10.34172/ijbsm.2023.06
102. Parisi GF, Manti S, Papale M, *et al.* Addition of a nutraceutical to montelukast or inhaled steroid in the treatment of wheezing during COVID-19 pandemic: A multicenter, open-label, randomized controlled trial. *Acta Biomed.* 2022;93(2):e2022156.
doi: 10.23750/abm.v93i2.11958
103. Soltani R, Nasirharandi S, Khorvash F, Nasirian M, Dolatshahi K, Hakamifard A. The effectiveness of gabapentin and gabapentin/montelukast combination compared with dextromethorphan in the improvement of COVID-19- related cough: A randomized, controlled clinical trial. *Clin Respir J.* 2022;16(9):604-610.
doi: 10.1111/crj.13529
104. Lima-Morales R, Méndez-Hernández P, Flores YN, *et al.* Effectiveness of a multidrug therapy consisting of Ivermectin, Azithromycin, Montelukast, and Acetylsalicylic acid to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico. *Int J Infect Dis.* 2021;105:598-605.
doi: 10.1016/j.ijid.2021.02.014
105. Salehi-Pourmehr H, Dolati S, Mehdipour R, *et al.* Effect of montelukast on treatment of coronavirus pneumonia (COVID-19): A systematic review. *Biomed Res Bull.* 2023;1(1):19-29.
doi: 10.34172/biomedrb.2023.06
106. Kerget B, Kerget F, Aydın M, Karaşahin Ö. Effect of montelukast therapy on clinical course, pulmonary function, and mortality in patients with COVID-19. *J Med Virol.* 2022;94(5):1950-1958.
doi: 10.1002/jmv.27552
107. Al-kuraishy HM, Al-Gareeb AI, Almulaiky YQ, Cruz-Martins N, El-Saber Batiha G. Role of leukotriene pathway and montelukast in pulmonary and extrapulmonary manifestations of Covid-19: The enigmatic entity. *Eur J Pharmacol.* 2021;904:174196.
doi: 10.1016/j.ejphar.2021.174196
108. Camera M, Canzano P, Brambilla M, Rovati GE. Montelukast inhibits platelet activation induced by plasma from COVID-19 patients. *Front Pharmacol.* 2022;13:784214.
doi: 10.3389/fphar.2022.784214
109. Salah HM, Mehta JL. Meta-analysis of the effect of aspirin on mortality in COVID-19. *Am J Cardiol.* 2021;142:158-159.
doi: 10.1016/j.amjcard.2020.12.073
110. Prieto-Campo Á, Zapata-Cachafeiro M, Portela-Romero M, Piñeiro-Lamas M, Figueiras A, Salgado-Barreira Á. Impact of prior use of antiplatelets on COVID-19 susceptibility, progression, and severity: A population-based study. *Rev Esp Cardiol Engl Ed.* 2024;77(7):539-546.
doi: 10.1016/j.rec.2023.12.004
111. Trimarco V, Izzo R, Pacella D, *et al.* Aspirin reduces the risk of type 2 diabetes associated with COVID-19. *NPJ Metabolic Health Dis.* 2025;3(1):27.
doi: 10.1038/s44324-025-00072-3
112. Abdelwahab HW, Shaltout SW, Sayed Ahmed HA, *et al.* Acetylsalicylic acid compared with enoxaparin for the prevention of thrombosis and mechanical ventilation in COVID-19 patients: A retrospective cohort study. *Clin Drug Investig.* 2021;41(8):723-732.
doi: 10.1007/s40261-021-01061-2
113. Chow JH, Khanna AK, Kethireddy S, *et al.* Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with coronavirus disease 2019. *Anesth Analg.* 2021;132(4):930-941.
doi: 10.1213/ANE.0000000000005292
114. Haji Aghajani M, Moradi O, Amini H, *et al.* Decreased in-hospital mortality associated with aspirin administration

- in hospitalized patients due to severe COVID-19. *J Med Virol.* 2021;93(9):5390-5395.
doi: 10.1002/jmv.27053
115. Su W, Miao H, Guo Z, Chen Q, Huang T, Ding R. Associations between the use of aspirin or other antiplatelet drugs and all-cause mortality among patients with COVID-19: A meta-analysis. *Front Pharmacol.* 2022;13:989903.
doi: 10.3389/fphar.2022.989903
116. Baral N, Mitchell JD, Savarapu PK, et al. All-cause and in-hospital mortality after aspirin use in patients hospitalized with COVID-19: A systematic review and meta-analysis. *Biol Methods Protoc.* 2022;7(1):bpac027.
doi: 10.1093/biomethods/bpac027
117. Wijaya I, Andhika R, Huang I, Purwiga A, Budiman KY. The effects of aspirin on the outcome of COVID-19: A systematic review and meta-analysis. *Clin Epidemiol Glob Health.* 2021;12:100883.
doi: 10.1016/j.cegh.2021.100883
118. Srinivasan A, Brown J, Krishnamani PP, et al. Aspirin use is associated with decreased inpatient mortality in patients with COVID-19: A meta-analysis. *Am Heart J Plus Cardiol Res Pract.* 2022;20:100191.
doi: 10.1016/j.ahjo.2022.100191
119. Zhao X, Gao C, Dai F, Treggiari MM, Deshpande R, Meng L. Treatments associated with lower mortality among critically ill COVID-19 patients: A retrospective cohort study. *Anesthesiology.* 2021;135(6):1076-1090.
doi: 10.1097/ALN.0000000000003999
120. Osborne TF, Veigulis ZP, Arreola DM, Mahajan SM, Rösli E, Curtin CM. Association of mortality and aspirin prescription for COVID-19 patients at the Veterans Health Administration. *PLoS One.* 2021;16(2):e0246825.
doi: 10.1371/journal.pone.0246825
121. Lal A, Garces JPD, Bansal V, et al. Pre-hospital aspirin use and patient outcomes in COVID-19: Results from the international viral infection and respiratory illness universal study (VIRUS). *Arch Bronconeumol.* 2022;58(11):746-753.
doi: 10.1016/j.arbres.2022.07.017
122. Meizlish ML, Goshua G, Liu Y, et al. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: A propensity score-matched analysis. *Am J Hematol.* 2021;96(4):471-479.
doi: 10.1002/ajh.26102
123. Iacobucci G. Covid-19: Aspirin does not improve survival for patients admitted to hospital, trial reports. *BMJ.* 2021;373:n1475.
doi: 10.1136/bmj.n1475
124. Ma S, Su W, Sun C, et al. Does aspirin have an effect on risk of death in patients with COVID-19? A meta-analysis. *Eur J Clin Pharmacol.* 2022;78(9):1403-1420.
doi: 10.1007/s00228-022-03356-5
125. Martha JW, Pranata R, Lim MA, Wibowo A, Akbar MR. Active prescription of low-dose aspirin during or prior to hospitalization and mortality in COVID-19: A systematic review and meta-analysis of adjusted effect estimates. *Int J Infect Dis.* 2021;108:6-12.
doi: 10.1016/j.ijid.2021.05.016
126. Liuzzo G, Patrono C. Can low-dose aspirin help the RECOVERY of patients hospitalized with COVID-19? *Eur Heart J.* 2022;43(8):714-715.
doi: 10.1093/eurheartj/ehab907
127. Liu Q, Huang N, Li A, et al. Effect of low-dose aspirin on mortality and viral duration of the hospitalized adults with COVID-19. *Medicine (Baltimore).* 2021;100(6):e24544.
doi: 10.1097/MD.00000000000024544
128. Santoro F, Núñez-Gil IJ, Vitale E, et al. Aspirin therapy on prophylactic anticoagulation for patients hospitalized with COVID-19: A propensity score-matched cohort analysis of the HOPE-COVID-19 registry. *J Am Heart Assoc.* 2022;11(13):e024530.
doi: 10.1161/JAHA.121.024530
129. Srivastava R, Kumar A. Use of aspirin in reduction of mortality of COVID-19 patients: A meta-analysis. *Int J Clin Pract.* 2021;75(11):e14515.
doi: 10.1111/ijcp.14515
130. Son M, Noh MG, Lee JH, Seo J, Park H, Yang S. Effect of aspirin on coronavirus disease 2019: A nationwide case-control study in South Korea. *Medicine (Baltimore).* 2021;100(30):e26670.
doi: 10.1097/MD.00000000000026670
131. Ali RM, Tharwat AI, Labib HA. Effect of aspirin use on clinical outcome among critically ill patients with COVID-19. *Egypt J Anaesth.* 2022;38(1):629-635.
doi: 10.1080/11101849.2022.2139104
132. Kumar GS, Vadgaonkar A, Purunaik S, et al. Efficacy and safety of aspirin, promethazine, and micronutrients for rapid clinical recovery in mild to moderate COVID-19 patients: A randomized controlled clinical trial. *Cureus.* 2022;14(5):e25467.
doi: 10.7759/cureus.25467
133. Azizi R, Dehghani Mobarakeh M, Goujani R, Nabi-Afjadi M, Mousavi Rizi S, Maghsoudi A. A study on the effect of aspirin on clinical symptoms, laboratory indices, and outcomes in patients with COVID-19. *J Nephropharmacol.* 2023;12(2):e10506.

- doi: 10.34172/npj.2023.10506
134. Ghati N, Bhatnagar S, Mahendran M, *et al.* Statin and aspirin as adjuvant therapy in hospitalised patients with SARS-CoV-2 infection: A randomised clinical trial (RESIST trial). *BMC Infect Dis.* 2022;22(1):606.
doi: 10.1186/s12879-022-07570-5
135. Gogtay M, Singh Y, Bullappa A, Scott J. Retrospective analysis of aspirin's role in the severity of COVID-19 pneumonia. *World J Crit Care Med.* 2022;11(2):92-101.
doi: 10.5492/wjccm.v11.i2.92
136. Campbell HM, Murata AE, Conner TA, Fotieo G. Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen and relationship with mortality among United States Veterans after testing positive for COVID-19. *PLoS One.* 2022;17(5):e0267462.
doi: 10.1371/journal.pone.0267462
137. Abani O, Abbas A, Abbas F, *et al.* Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. *Lancet.* 2022;399(10320):143-151.
doi: 10.1016/S0140-6736(21)01825-0
138. Mina J, Fleifel M, Haykal T, *et al.* Effect of combination of prophylactic or therapeutic anticoagulation with aspirin on the outcomes of hospitalized COVID-19 patients: An observational retrospective study. *Medicine (Baltimore).* 2023;102(25):e34040.
doi: 10.1097/MD.00000000000034040
139. Yuan S, Chen P, Li H, Chen C, Wang F, Wang DW. Mortality and pre-hospitalization use of low-dose aspirin in COVID-19 patients with coronary artery disease. *J Cell Mol Med.* 2021;25(2):1263-1273.
doi: 10.1111/jcmm.16198
140. Sahai A, Bhandari R, Godwin M, *et al.* Effect of aspirin on short-term outcomes in hospitalized patients with COVID-19. *Vasc Med.* 2021;26(6):626-632.
doi: 10.1177/1358863X211012754
141. Botton J, Semenzato L, Dupouy J, *et al.* No association of low-dose aspirin with severe COVID-19 in France: A cohort of 31.1 million people without cardiovascular disease. *Res Pract Thromb Haemost.* 2022;6(4):e12743.
doi: 10.1002/rth2.12743
142. Vinod P, Krishnappa V, Rathell W, *et al.* Effect of aspirin use on the adverse outcomes in patients hospitalized for COVID-19. *Cardiol Res.* 2024;15(3):179-188.
doi: 10.14740/cr1645
143. Xue L, Qi Y, Zou Y. Short-term safety and efficacy of aspirin in patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. *PeerJ.* 2025;13:e19466.
doi: 10.7717/peerj.19466
144. Elgendy H, Ganaw A, Kumari V, *et al.* Risk factors influence the arterial line patency in ICU-bound patients during COVID-19 pandemic: An observational cohort study. *Egypt J Anaesth.* 2023;39(1):401-411.
doi: 10.1080/11101849.2023.2209411
145. Sullerot C, Bouiller K, Laborde C, *et al.* Premorbid aspirin use is not associated with lower mortality in older inpatients with SARS-CoV-2 pneumonia. *GeroScience.* 2022;44(2):573-583.
doi: 10.1007/s11357-021-00499-8
146. Zekri-Nechar K, Barberán J, Zamorano-León JJ, *et al.* Analysis of prior aspirin treatment on in-hospital outcome of geriatric COVID-19 infected patients. *Medicina.* 2022;58(11):1649.
doi: 10.3390/medicina58111649
147. Kim I, Yoon S, Kim M, *et al.* Aspirin is related to worse clinical outcomes of COVID-19. *Medicina (Kaunas).* 2021;57(9):931.
doi: 10.3390/medicina57090931
148. Morrison FJ, Su M, Turchin A. COVID-19 outcomes in patients taking cardioprotective medications. *PLoS One.* 2022;17(10):e0275787.
doi: 10.1371/journal.pone.0275787
149. Ware AD, Veigulis ZP, Hoover PJ, *et al.* Incidence and risk of post-COVID-19 thromboembolic disease and the impact of aspirin prescription; nationwide observational cohort at the US Department of Veteran Affairs. *PLoS One.* 2024;19(9):e0302612.
doi: 10.1371/journal.pone.0302612
150. Eikelboom JW, Jolly SS, Belley-Cote EP, *et al.* Colchicine and the combination of rivaroxaban and aspirin in patients hospitalised with COVID-19 (ACT): An open-label, factorial, randomised, controlled trial. *Lancet Respir Med.* 2022;10(12):1169-1177.
doi: 10.1016/S2213-2600(22)00298-3
151. Basheer M, Saad E, Hagai R, Assy N. Clinical predictors of mortality and critical illness in patients with COVID-19 pneumonia. *Metabolites.* 2021;11(10):679.
doi: 10.3390/metabo11100679
152. Merzon E, Green I, Vinker S, *et al.* The use of aspirin for primary prevention of cardiovascular disease is associated with a lower likelihood of COVID-19 infection. *FEBS J.* 2021;288(17):5179-5189.
doi: 10.1111/febs.15784
153. Paules CI, Nordwall JA, Shaw-Saliba K, *et al.* Blood absolute lymphocyte count and trajectory are important in understanding severe COVID-19. *BMC Infect Dis.* 2025;25(1):67.

- doi: 10.1186/s12879-024-10428-7
154. Yan X, Hao Q, Mu Y, *et al.* Retraction notice to “Nucleocapsid protein of SARS-CoV activates the expression of cyclooxygenase-2 by binding directly to regulatory elements for nuclear factor-kappa B and CCAAT/enhancer binding protein” [Int J Biochem Cell Biol. 2006;38:1417-1428]. *Int J Biochem Cell Biol.* 2024;176:106674.
doi: 10.1016/j.biocel.2024.106674
155. Liu M, Yang Y, Gu C, *et al.* RETRACTED: Spike protein of SARS-CoV stimulates cyclooxygenase-2 expression via both calcium-dependent and calcium-independent protein kinase C pathways. *FASEB J.* 2007;21(7):1586-1596.
doi: 10.1096/fj.06-6589com
156. Wang X, Lu J, Ge S, *et al.* Astemizole as a drug to inhibit the effect of SARS-COV-2 *in vitro*. *Microb Pathog.* 2021;156:104929.
doi: 10.1016/j.micpath.2021.104929
157. Konrat R, Papp H, Kimpel J, *et al.* The anti-histamine azelastine, identified by computational drug repurposing, inhibits infection by major variants of SARS-CoV-2 in cell cultures and reconstituted human nasal tissue. *Front Pharmacol.* 2022;13:861295.
doi: 10.3389/fphar.2022.861295
158. Fischhuber K, Bánki Z, Kimpel J, *et al.* Antiviral potential of azelastine against major respiratory viruses. *Viruses.* 2023;15(12):2300.
doi: 10.3390/v15122300
159. Ge S, Lu J, Hou Y, Lv Y, Wang C, He H. Azelastine inhibits viropexis of SARS-CoV-2 spike pseudovirus by binding to SARS-CoV-2 entry receptor ACE2. *Virology.* 2021;560:110-115.
doi: 10.1016/j.virol.2021.05.009
160. Westover JB, Ferrer G, Vazquez H, Bethencourt-Mirabal A, Go CC. *In vitro* virucidal effect of intranasally delivered chlorpheniramine maleate compound against severe acute respiratory syndrome coronavirus 2. *Cureus.* 2020;12(9):e10501.
doi: 10.7759/cureus.10501
161. Yang H, George SJ, Thompson DA, *et al.* Famotidine activates the vagus nerve inflammatory reflex to attenuate cytokine storm. *Mol Med.* 2022;28(1):57.
doi: 10.1186/s10020-022-00483-8
162. Rivas MD, Maria J, Zamorano J. *Hydroxyzine Inhibits SARS-CoV-2 Spike Protein Binding to ACE2 in a Qualitative in Vitro Assay.* *bioRxiv.* New York: Cold Spring Harbor Laboratory; 2021.
doi: 10.1101/2021.01.04.424792
163. Kiani P, Scholey A, Dahl TA, McMann L, Iversen JM, Verster JC. *In vitro* assessment of the antiviral activity of ketotifen, indomethacin and naproxen, alone and in combination, against SARS-CoV-2. *Viruses.* 2021;13(4):559.
doi: 10.3390/v13040558
164. Hou Y, Ge S, Li X, Wang C, He H, He L. Testing of the inhibitory effects of loratadine and desloratadine on SARS-CoV-2 spike pseudotyped virus viropexis. *Chem Biol Interact.* 2021;338:109420.
doi: 10.1016/j.cbi.2021.109420
165. Morin-Dewaele M, Bartier S, Berry F, *et al.* Desloratadine, an FDA-approved cationic amphiphilic drug, inhibits SARS-CoV-2 infection in cell culture and primary human nasal epithelial cells by blocking viral entry. *Sci Rep.* 2022;12(1):21053.
doi: 10.1038/s41598-022-25399-5
166. Di Petrillo A, Orrù G, Fais A, Fantini MC. Quercetin and its derivatives as antiviral potentials: A comprehensive review. *Phytother Res.* 2022;36(1):266-278.
doi: 10.1002/ptr.7309
167. Cagno V, Magliocco G, Tapparel C, Daali Y. The tyrosine kinase inhibitor nilotinib inhibits SARS-CoV-2 *in vitro*. *Basic Clin Pharmacol Toxicol.* 2021;128(4):621-624.
doi: 10.1111/bcpt.13537

Appendix

Table A1. Summary of literature search results

Generic name	PubMed (n)	Directory of Open Access Journals (n)	Europe PMC (n)
Antazoline	0	0	14
Aspirin	413	149	12,113
Astemizole	1	1	155
Azelastine	16	8	179
Bepotastine	0	0	43
Bilastine	3	2	102
Brompheniramine	1	1	30
Carbinoxamine maleate	3	0	12
Cetirizine	15	5	880
Chlorpheniramine	10	4	305
Cimetidine	9	5	461
Cinnarizine	1	0	50
Clemastine	3	0	190
Cromoglicic acid	1	1	26
Cromolyn sodium	2	1	99
Cyproheptadine	4	3	225
Dasatinib	34	18	1,277
Desloratadine	0	0	8
Dexbrompheniramine	1	0	5
Dexchlorpheniramine	2	0	96
Dimenhydrinate	0	0	110
Diphenhydramine	22	12	2,524
Doxepin	1	0	279
Doxylamine	0	0	86
Ebastine	8	2	170
Emedastine	0	0	11
Famotidine	84	28	1,166

(Cont'd...)

Table A1. (Continued)

Generic name	PubMed (n)	Directory of Open Access Journals (n)	Europe PMC (n)
Fexofenadine	8	9	360
Hydroxyzine	12	5	534
Ibudilast	2	0	102
Ketotifen	3	2	174
Levocetirizine	4	3	192
Lodoxamide	0	0	12
Loratadine	14	6	488
Luteolin	162	58	2,291
Meclizine	4	2	100
Midostaurin	4	4	252
Mizolastine	2	0	27
Montelukast	57	31	1,167
Nedocromil	0	0	50
Nilotinib	27	14	726
Nizatidine	1	0	62
Olopatadine	3	1	74
Pemrolast	1	0	41
Pheniramine	3	0	70
Pranlukast	1	1	65
Promethazine	4	4	500
Quercetin	350	166	5,607
Ranitidine	7	2	512
Rupatadine	5	0	108
Spaglumic acid	0	0	2
Terfenadine	3	2	170
Triprolidine	0	0	75
Verlukast	0	0	1
Zafirlukast	8	4	174
Zileuton	2	2	48